Attorney Docket No. PO2019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Nicholas S. Bodor
U.S. Patent No.:	:	4,996,335
Issue Date	:	February 26, 1991
Application Serial No.	:	807,034
Application Filing Date	:	December 9, 1985
Inventor	:	NICHOLAS S. BODOR
For	:	SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

Pursuant to 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, and in accordance with the provisions of 35 USC 156, Nicholas S Bodor, residing at 6219 S. W. 93rd Avenue, Gainesville, Florida 32608 (hereinafter referred to as "Applicant"), the assignee of record of United States Patent No. 4,996,335, hereby applies for an extension of 1,284 days of the term of United States Patent No. 4,996,335, issued February 26, 1991 on patent application Serial No. 807,034 filed December 9, 1985.

The following information is submitted in accordance with 35 USC S 156(d) and 37 CFR § 1.740, and follows the numerical format set forth in 37 CFR § 1.740.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved products are LOTEMAX™ and ALREX™. The active ingredient in both LOTEMAX™ and ALREX™ is loteprednol etabonate.

LOTEMAX™ is a trademark of Pharmos Corporation, having an office at 33 Wood Avenue South, Ste. 466, Iselin, New Jersey 08830. Pharmos Corporation has been licensed in the United States by Applicant under United States Patent No. 4,996,335. A LETTER OF THE LICENSEE (Exhibit A), of Pharmos Corporation, is being submitted concomitantly herewith which provides authorization to Applicant to rely on the activities and data of Pharmos Corporation, before the Food and Drug Administration in obtaining approval of the drugs LOTEMAX™ and ALREX™ for the purpose of obtaining a patent term extension for United States Patent No. 4,996,335.

ALREX™ is a trademark of Bausch & Lomb Pharmaceuticals, Inc, which has a place of business at 8500 Hidden River Parkway, Tampa, FL 33637. Bausch & Lomb Pharmaceuticals, Inc., has been sub-licensed in the United States by Pharmos Corporation under United States Patent No. 4,996,335. A LETTER OF THE SUB-LICENSEE (Exhibit B), of Bausch & Lomb Pharmaceuticals, Inc., is being submitted concomitantly herewith which provides authorization to Applicant to rely on the activities and data of Bausch & Lomb Inc., including its wholly owned subsidiary Bausch & Lomb Pharmaceuticals, Inc., before the Food and Drug Administration in

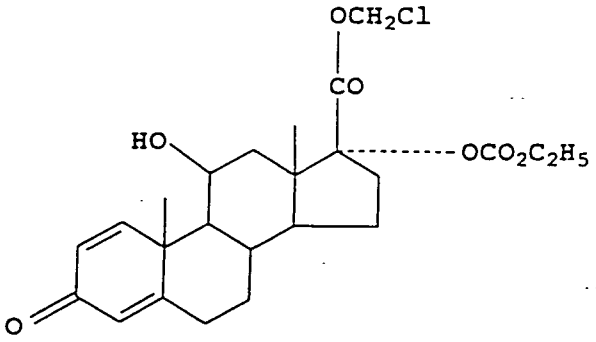
obtaining approval of the drugs LOTEMAX™ and ALREX™ for the purpose of obtaining a patent term extension for United States Patent No. 4,996,335.

Loteprednol etabonate is designated chemically as chloromethyl-17α-[(ethoxycarbonyl) oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate. Loteprednol etabonate can also be designated chemically as chloromethyl-17α-ethoxycarbonyloxy-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate.

The empirical formula of loteprednol etabonate is $C_{24}H_{31}ClO_7$ and has a molecular weight of 466.96 daltons.

Loteprednol etabonate is also known as "P-5604" (internal code designation).

The plane structural formula of loteprednol etabonate is as follows:



LOTEMAX™ (loteprednol etabonate) and ALREX™ (loteprednol etabonate) are both a pharmaceutical for topical ophthalmic administration. The Product Information sheet for the approved product (hereinafter the term "product" or "approved product" refers to

both LOTEMAX™ and ALREX™) is the PACKAGE INSERT. A copy of the PACKAGE INSERT for LOTEMAX™ is attached as Exhibit C. A copy of the PACKAGE INSERT for ALREX™ is attached as Exhibit D.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under § 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 USC § 301 et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

LOTEMAX™ (loteprednol etabonate) and ALREX™ (loteprednol etabonate) were all approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to § 505(b) of the FFDCA on March 9, 1998; see Exhibit E (APPROVAL LETTER for LOTEMAX™), Exhibit F (APPROVAL LETTER for ALREX™), and Exhibit G (APPROVAL LETTER FOR LOTEMAX™).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in both LOTEMAX™ and ALREX™ is loteprednol etabonate. Neither loteprednol etabonate, nor any form of loteprednol etabonate have been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to S 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on March 9,1998, and the last day within the sixty (60) day period permitted for submission of an application for extension (pursuant to 37 CFR 1.720(f)) of the patent is May 7, 1998. The date of submission of the present application is no later than May 7, 1998, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. Patent No.	:	4,996,335
Issue Date	:	February 26, 1991
Inventors	:	NICHOLAS S. BODOR
Title	:	SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY
Application Serial No.	:	807,034
Application Filing Date	:	December 9, 1985
Expiration Date (unless extended)	:	February 26, 2008

The application is assigned from Otsuka Pharmaceuticals Co., Ltd., to the Applicant by an assignment recorded on July 15, 1988, in the United States Patent and Trademark Office at Reel 4914, Frame 0693 . A copy of the recorded assignment is attached as Exhibit H.

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent 4,996,335 is attached as Exhibit I (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

No disclaimer or reexamination certificate has been issued.

A Certificate of Correction for United States Patent No. 4,996,335 was filed on March 23, 1998. A copy of said Certificate of Correction, including the Request therefor and an acknowledgment postcard from the U.S. Patent and Trademark Office is attached herewith as Exhibit J.

A maintenance fee payment was made to the U.S. Patent and Trademark Office for United States Patent No. 4,996,335 on September 8, 1994. A copy of the receipt for such maintenance fee payment, received from the Patent and Trademark Office, is attached hereto as Exhibit K.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

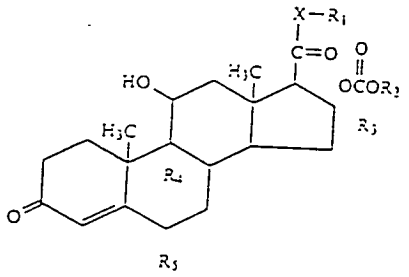
United States Patent No. 4,996,335 claims loteprednol etabonate (LOTEMAX™ and ALREX™). Both LOTEMAX™ and ALREX™ are in ophthalmic suspension form. LOTEMAX™ is approved as a loteprednol etabonate ophthalmic suspension, 0.5%. ALREX™ is approved as a loteprednol etabonate ophthalmic suspension, 0.2%.

Claims 1, 2, 3, 10, 12, 13, 14, 15, 17, 18, 19, 20, 26, 27, 28, 29, 30,31, 32, 33, 69

88, 89, 90, 104, 110 and 111, which were allowed in United States Patent No. 4,996,335, each includes loteprednol etabonate within its scope. Note in particular the structural formulae set out in Claims 2 and 110 in United States Patent No. 4,996,335, as corrected by the Request for Certificate of Correction filed March 23, 1998.

Claims 1 to 3, 10, 12 to 15, 17 to 20, 26 to 33, 69, 88 to 90, 104, 110 and 111 of United States Patent No. 4,996,335 *are* set forth as follows:

1. A compound selected from the group consisting of:
(a) a compound of the formula



(I)

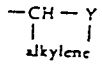
wherein:
R_1 is C_1–C_{10} alkyl; C_2–C_{10} (monohydroxy or polyhydroxy)alkyl; C_1–C_{10} (monohalo or polyhalo)alkyl; or $—CH_2COOR_6$ wherein R_6 is unsubstituted or substituted C_1–C_{10} alkyl; C_3–C_8 cycloalkyl, C_3–C_8 cycloalkenyl or C_2–C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,

$$—NHC(=O)—(C_1\text{–}C_{10}\ \text{alkyl})\quad\text{and}\quad —OC(=O)—(C_1\text{–}C_{10}\ \text{alkyl}).$$

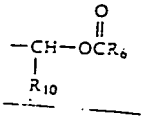
or R_6 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carabamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl-)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R_1 is $—CH_2CONR_7R_8$ wherein R_7 and R_8, which can be the same or different, are each hydrogen, lower alkyl, C_3–C_8 cycloalkyl, phenyl or benzyl, or R_7 and R_8 are combined such that $—NR_7R_8$ represents the residue of a saturated monocyclic secondary amine; or R_1 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to R_6; or R_1 is

$$—CH(R_9)—Y\text{-(lower alkyl)}$$

wherein Y is —S—, —SO—, —SO_2— or —O— and R_9 is hydrogen, lower alkyl or phenyl, or R_9 and the lower alkyl group adjacent to Y are combined so that R_1 is a cyclic system of the type

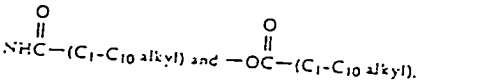


wherein Y is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms; or R_1 is



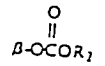
wherein R_6 is defined as hereinabove and R_{10} is hydrogen, lower alkyl, phenyl or halophenyl;

R_2 is unsubstituted or substituted C_1–C_{10} alkyl, C_3–C_8 cycloalkyl, C_3–C_8 cycloalkenyl or C_2–C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,



or R_2 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl;

R_3 is hydrogen, α-hydroxy, β-hydroxy, α-methyl, β-methyl, $=CH_2$, or α- or



wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen, fluoro or chloro;

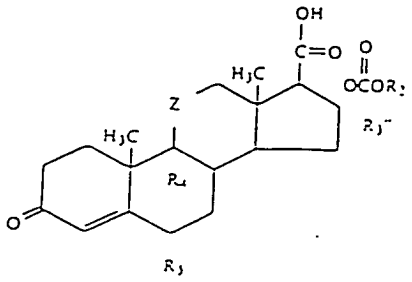
R_5 is hydrogen, fluoro, chloro or methyl;

X is —O— or —S—;

and the dotted line in ring A indicates that the 1,2 linkage is saturated or unsaturated;

(b) a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group;

(c) a compound of the formula

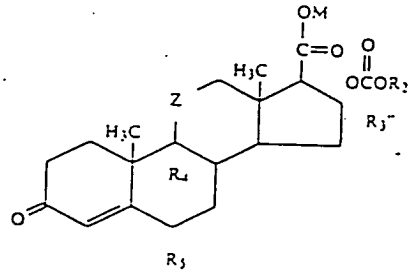


(III)

wherein R_2, R_4, R_5, and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β-hydroxymethylene and R_3'' is hydrogen, α-methyl, β-methyl, $=CH_2$ or α- or

wherein R_2 is identical to R_2 above;

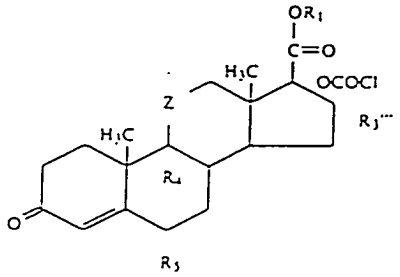
(d) a compound of the formula



(IV)

wherein M is alkali metal, thallium, alkaline earth metal/2 or NH_4 and R_2, R_3'', R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

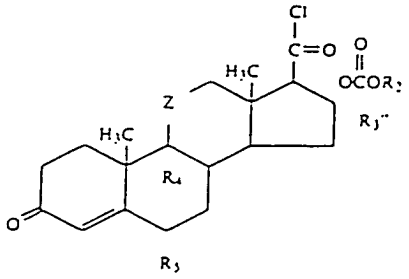
(e) a compound of the formula



(VII)

wherein R_3''' is hydrogen, α-methyl, β-methyl, α-OCOCl or β-OCOCl, and R_1, R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

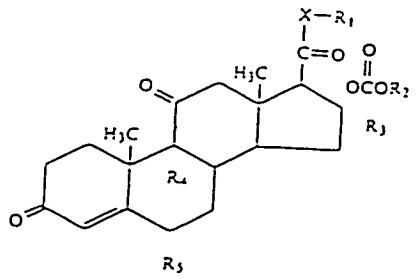
(f) a compound of the formula



(VIII)

wherein R_2, R_3'', R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above; and

(g) a compound of the formula

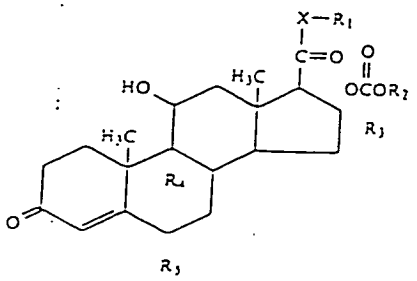


(IX)

wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in ring A are as defined in (a) above.

2. A compound selected from the group consisting of:

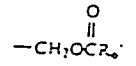
(a) a compound of the formula



(I)

wherein:

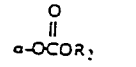
R_1 is C_1-C_6 alkyl; C_1-C_6 (monohalo or polyhalo)alkyl; $-CH_2COOR_6$ wherein R_6 is C_1-C_6 alkyl; $-CH_2-Y-(C_1$-C_6 alkyl) wherein Y is —S—, —SO—, $-SO_2-$ or —O—; or



wherein R_6' is C_1-C_6 or phenyl;

R_2 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl;

R_3 is hydrogen, α-hydroxy, β-methyl, β-methyl or



wherein R_2' is identical to R_2 as defined hereinabove;

R_4 is hydrogen or fluoro;

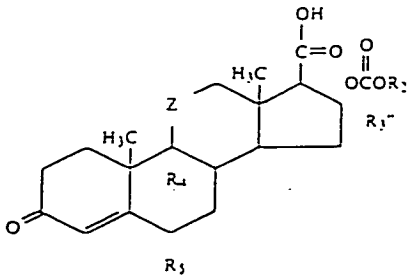
R_5 is hydrogen or fluoro;

X is —O—;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated;

(b) a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group;

(c) a compound of the formula

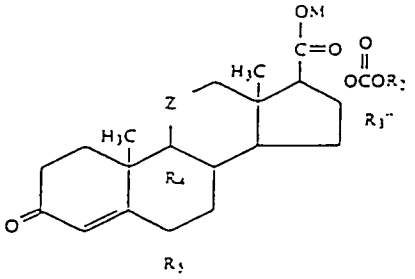


(III)

wherein R_2, R_4, R_5 and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β-hydroxymethylene and R_3'' is hydrogen, α-methyl, β-methyl or

wherein R_2 is identical to R_2 above;

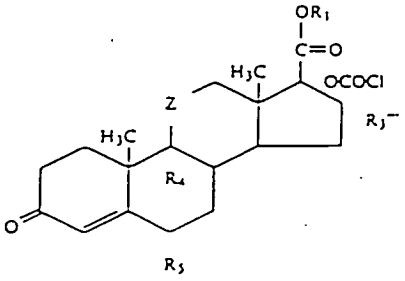
(d) a compound of the formula



(IV)

wherein M is alkali metal, thallium, alkaline earth metal/2 or NH_4 and R_2, R_3'', R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

(e) a compound of the formula

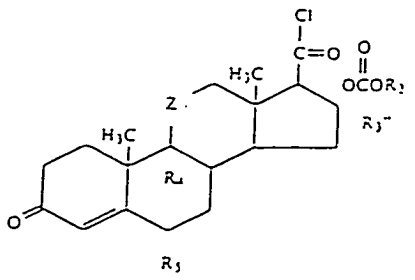


(VII)

wherein R_3''' is hydrogen, α-methyl, β-methyl or α-OCOCl, and R_1, R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

(f) a compound of the formula

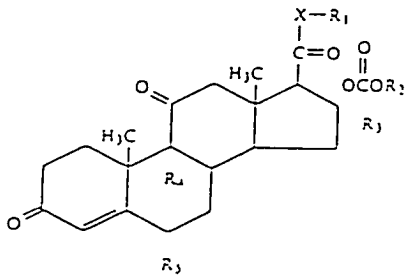
(VIII)



wherein R_2, R_3'', R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above; and

(g) a compound of the formula

(IX)



wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in ring A are as defined in (a) above.

3. A compound of claim 1 or 2, said compound having the structural formula (I).

10. A compound of claim 1, said compound having the structural formula (I) wherein R_3 is hydrogen, α-methyl, β-methyl, $=CH_2$ or α- or

β-$OCOR_3$.

12. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_1 is C_1-C_6 (monohalo or polyhalo)alkyl.

13. A compound of claim 12 wherein C_1-C_6 (monohalo or polyhalo)alkyl is C_1-C_6 monohaloalkyl.

14. A compound of claim 13 wherein C_1-C_6 monohaloalkyl is C_1-C_6 monochloroalkyl.

15. A compound of claim 14 wherein C_1-C_6 monochloroalkyl is chloromethyl.

17. A compound of claim 12 wherein R_2 is C_1-C_6 alkyl.

18. A compound of claim 13 wherein R_2 is C_1-C_6 alkyl.

19. A compound of claim 14 wherein R_2 is C_1-C_6 alkyl.

20. A compound of claim 15 wherein R_2 is C_1-C_6 alkyl.

26. A compound of claim 1, said compound having the structural formula (I) wherein X is —O—.

27. A compound of claim 12 wherein X is —O—.

28. A compound of claim 13 wherein X is —O—.

29. A compound of claim 14 wherein X is —O—.

30. A compound of claim 17 wherein R_4 and R_5 are hydrogen.

31. A compound of claim 18 wherein R_4 and R_5 are hydrogen.

32. A compound of claim 19 wherein R_4 and R_5 are hydrogen.

33. A compound of claim 20 wherein R_4 and R_5 are hydrogen.

69. The compound of claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate.

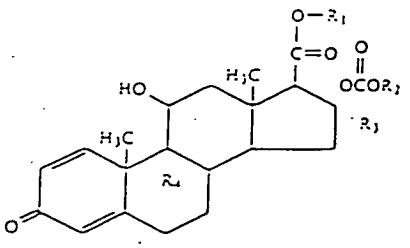
88. A pharmaceutical composition of matter comprising an anti-inflammatory effective amount of a compound of claim 1 or 2 having the structural formula (I), in combination with a non-toxic pharmaceutically acceptable carrier therefor suitable for topical or other local application.

89. A method for alleviating inflammation in or on a warm-blooded animal exhibiting a topical inflammatory response, which comprises topically administering thereto an anti-inflammatory effective amount of a composition of claim 88.

90. A method for alleviating inflammation in or on a warm-blooded animal exhibiting a localized inflammatory response, which comprises locally administering thereto an anit-inflammatory effective amount of composition of claim 88.

104. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_3, R_4 and R_5 are hydrogen and the 1,2 linkage is saturated or unsaturated.

110. A compound of the formula

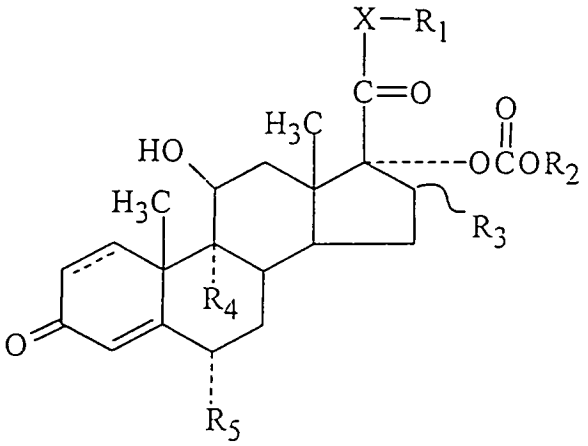


wherein R_1 is C_1–C_5 (monohalo)alkyl, R_2 is C_1–C_5 alkyl, R_3 is hydrogen, α-methyl or β-methyl and R_4 is hydrogen or fluoro.

111. A compound of claim 110 wherein R_1 is chloromethyl.

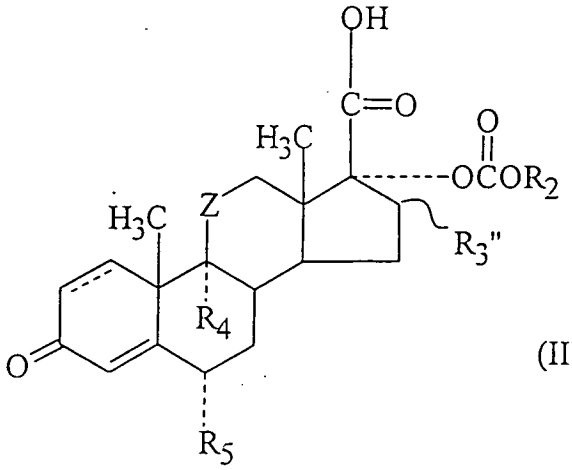
Claims 1, 2 and 110 of the claims set forth above contain a number of errors which occurred during printing. The corrections set forth in the Request for Certificate of Correction for this group of claims covering loteprednol etabonate are the following set forth on pages 23-29 of the Request for Certificate of Correction:

In Column 80, lines 2-12, part (a) of Claim 1, delete the structural formula (I) and insert in its stead:



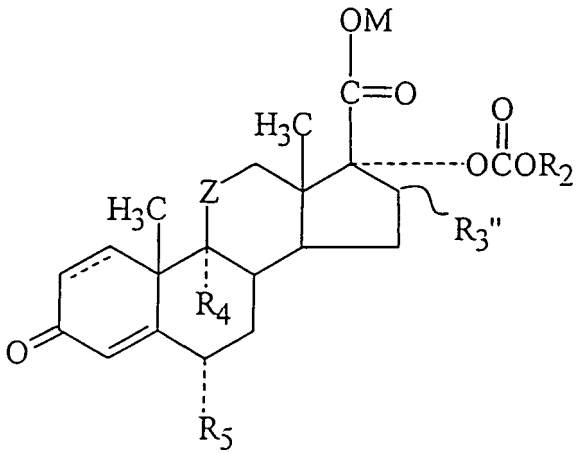
(I)

In Column 81, lines 55-65, part (c) of Claim 1, delete the structural formula and insert in its stead:



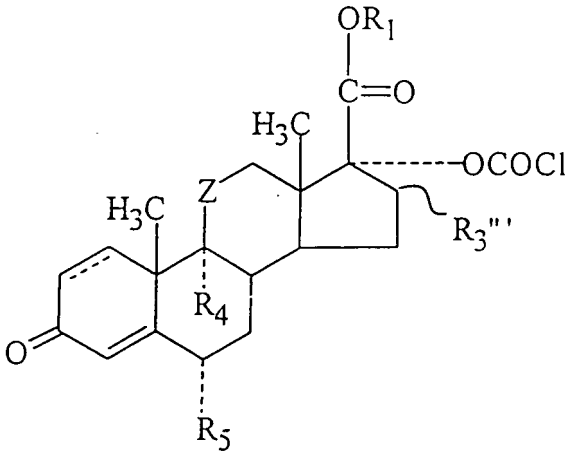
(III)

In Column 82, lines 15-24, part (d) of Claim 1, delete the structural formula (IV) and insert in its stead:



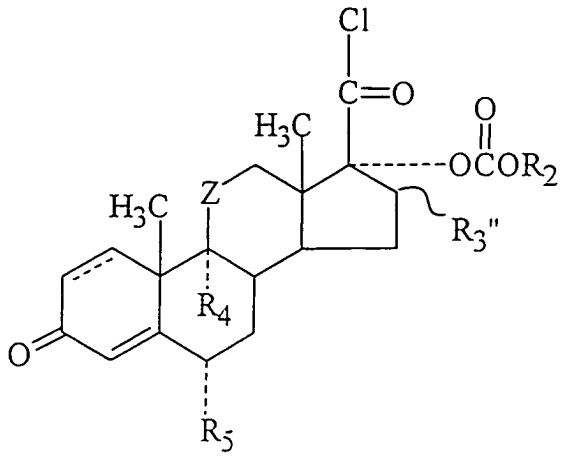
(IV)

In Column 82, lines 34-44, part (e) of Claim 1, delete the structural formula (VII) and insert in its stead:



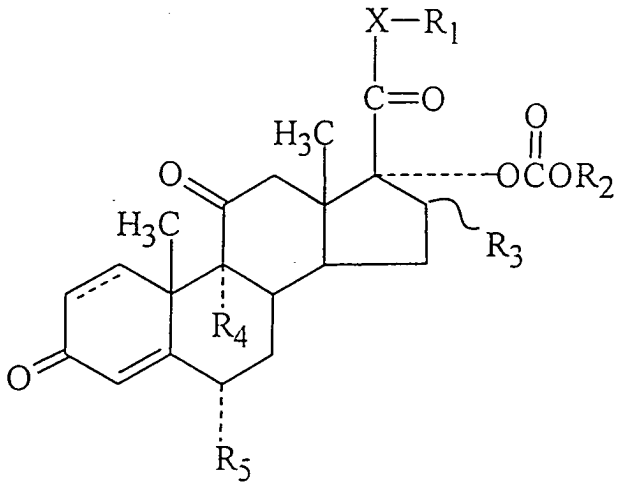
(VII)

In Column 82, lines 53-64, part (f) of Claim 1, delete the structural formula (VIII) and insert in its stead:



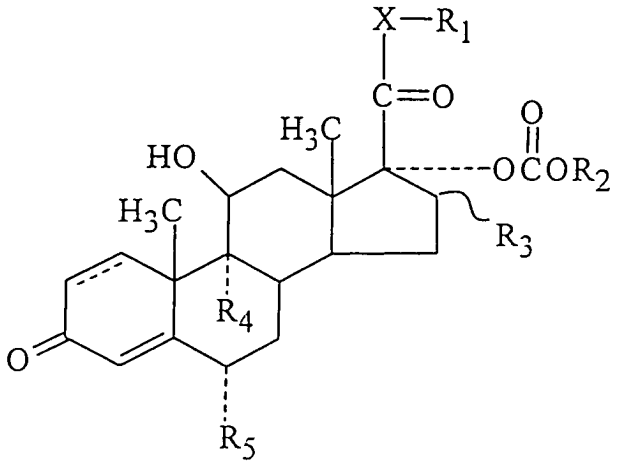
(VIII)

In Column 83, lines 2-12, part (g) of Claim 1, delete the structural formula (IX) and insert in its stead:



(IX)

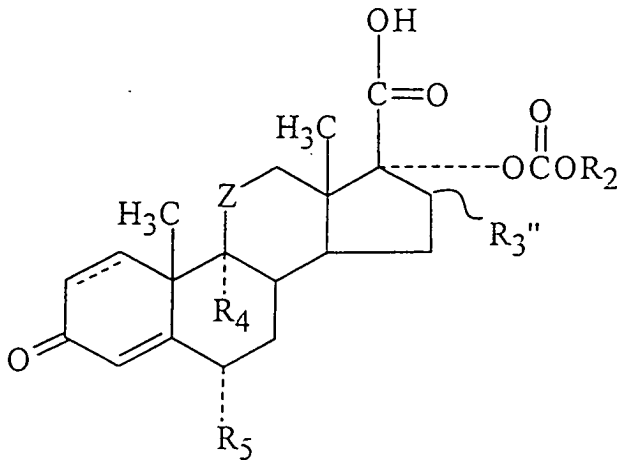
In Column 83, lines 20-31, part (a) of Claim 2, delete the structural formula (I) and insert in its stead:



(I)

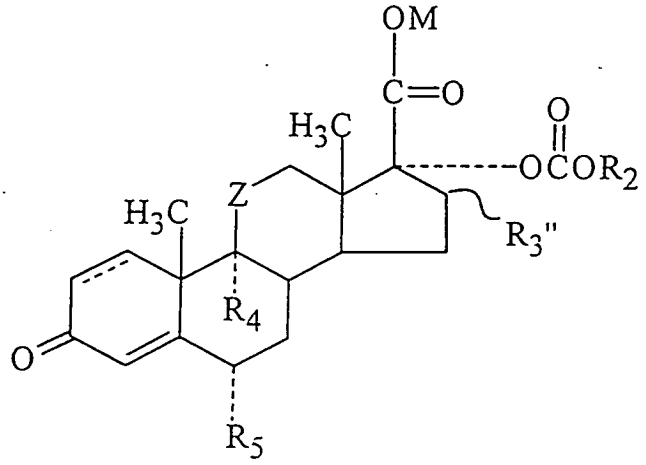
In Column 83, line 49, part (a) of Claim 2, in the definition of R_3, "β-methyl, β-methyl" should read --α-methyl, β-methyl--.

In Column 84, lines 2-13, part (c) of Claim 2, delete the structural formula (III) and insert in its stead:



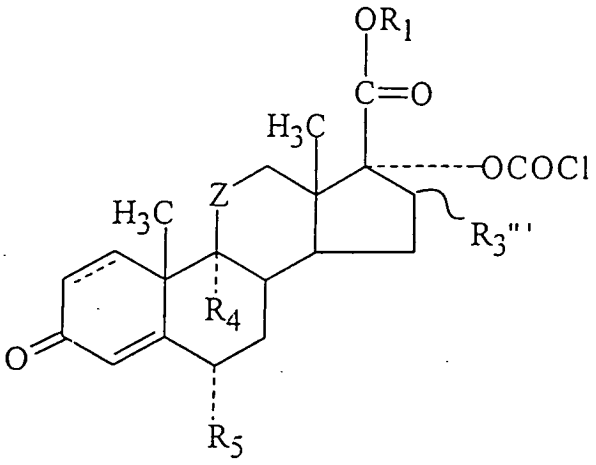
(III)

In Column 84, lines 31-43, part (d) of Claim 2, delete the structural formula (IV) and insert in its stead:



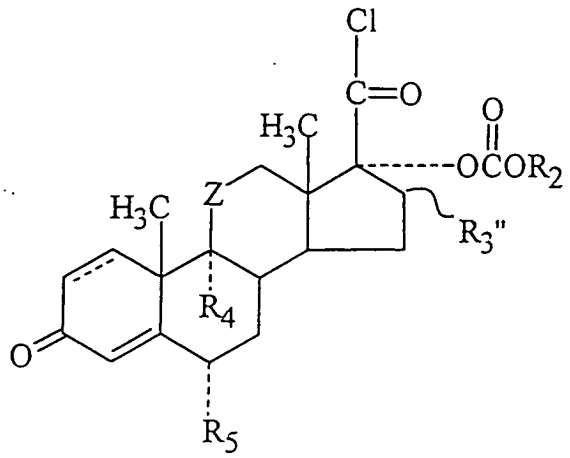
(IV)

In Column 84, lines 51-62, part (e) of Claim 2, delete the structural formula (VII) and insert in its stead:



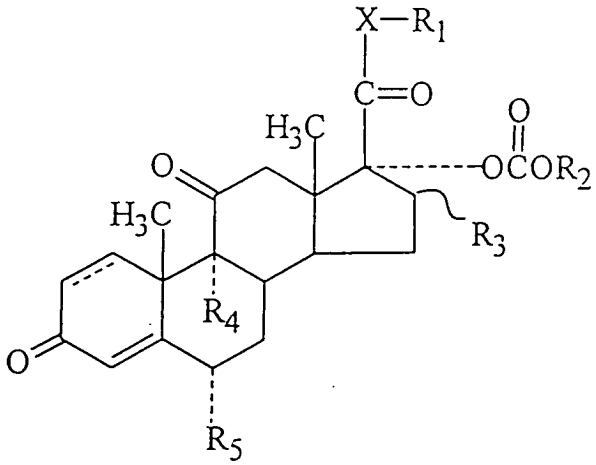
(VII)

In Column 85, lines 2-12, part (f) of Claim 2, delete the structural formula (VIII) and insert in its stead:



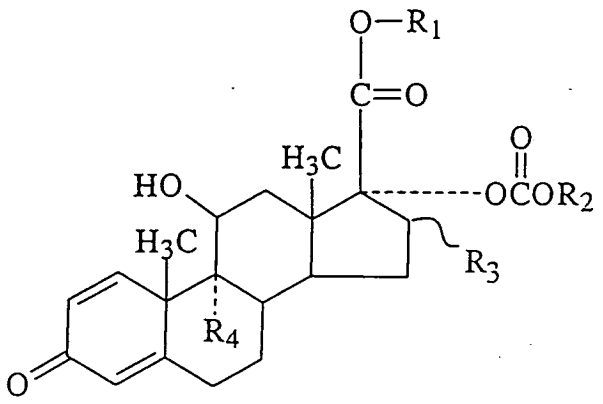
(VIII)

In Column 85, lines 18-28, part (g) of Claim 2, delete the structural formula (IX) and insert in its stead:



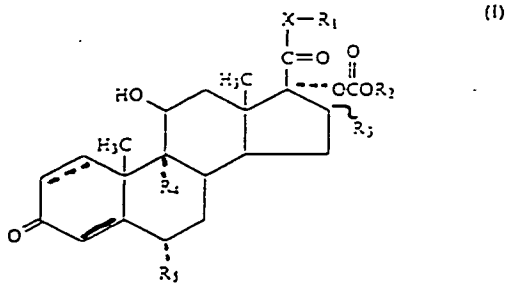
(IX)

In Column 90, lines 33-42, Claim 110, delete the structural formula and insert in its stead:



Claim 1

Claim 1, as amended in the Request for Certificate of Correction to reflect correction of printing errors, recites compounds of the formula

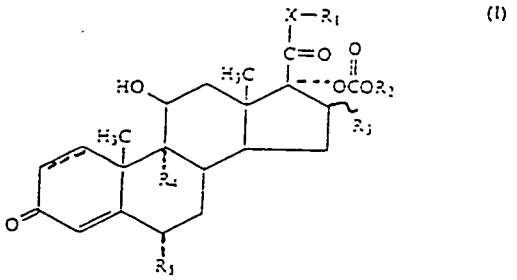


(I)

wherein R_1 can be C_1-C_{10} (monohalo or polyhalo) alkyl, R_2 can be unsubsituted C_1-C_{10} alkyl, R_3, R_4 and R_5 can be hydrogen, X can be oxygen, and the dotted line in ring A indicates that the 1, 2 linkage can be unsaturated. This structure has been corrected to show all missing dotted and wavy lines. Thus Claim 1 covers loteprednol etabonate.

Claim 2

Claim 2 , as amended in the Request for Certificate of Correction to reflect correction of printing errors, recites compounds of the formula



(I)

wherein R_1 can be C_1-C_6 (monohalo or polyhalo) alkyl, R_2 can be C_1-C_6 alkyl, R_3, R_4, R_5, can be hydrogen, X can be oxygen, and the dotted line in ring A indicates that the 1, 2 linkage can be unsaturated. This structure has been corrected to show all missing dotted and wavy lines. Thus Claim 2 covers loteprednol etabonate.

Claim 3

In Claim 3, which depends on Claims 1 or 2, the compound has structural formula (I) and R_1, R_2, R_3, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 3 covers loteprednol etabonate.

Claim 10

In Claim 10, which depends on Claim 1, the compound has structural formula (I) and R_1,

Claim 12

In Claim 12, which depends on Claims 1 or 2, the compound has structural formula (I), R_1 can be C_1-C_6 (monohalo or polyhalo) alkyl and R_1, R_2, R_3, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 12 covers loteprednol etabonate.

Claim 13

In Claim 13, which depends on Claim 12, R_1 can be C_1-C_6 monohaloalkyl and R_2, R_3, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 13 covers loteprednol etabonate.

Claim 14

In Claim 14, which depends on Claim 13, R_1 can be C_1-C_6 monochloroalkyl and R_2, R_3, R_4, R_5 , X and the dotted line in the A ring are as previously defined. Thus Claim 14 covers loteprednol etabonate.

Claim 15

In Claim 15, which depends on Claim 14, R_1 can be chloromethyl and R_2, R_3, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 15 covers loteprednol etabonate.

Claim 17

In Claim 17, which depends on Claim 12, R_2 can be C_1-C_6 alkyl and R_1, R_3, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 17 covers loteprednol etabonate.

Claim 18

In Claim 18, which depends on Claim 13, R_2 can be C_1-C_6 alkyl and R_1, R_3, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 18 covers loteprednol etabonate.

Claim 19

In Claim 19, which depends on Claim 14, R_2 can be C_1-C_6 alkyl and R_1, R_3, R_4, R_5, X and the dotted line in the A ring and the dotted line in the A ring are as previously defined. Thus Claim 19 covers loteprednol etabonate.

Claim 20

In Claim 20, which depends on Claim 15, R_2 can be C_1-C_6 alkyl and R_1, R_3, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 20 covers loteprednol etabonate.

Claim 26

In Claim 26, which depends on Claim 1, X can be oxygen and R_1, R_2 R_3, R_4, R_5 and the dotted line in the A ring are as previously defined. Thus Claim 26 covers loteprednol etabonate.

Claim 27

In Claim 27, which depends on Claim 12, X can be oxygen and R_1, R_2 R_3, R_4, R_5 and the dotted line in the A ring are as previously defined. Thus Claim 27 covers loteprednol etabonate.

Claim 28

In Claim 28, which depends on Claim 13, X can be oxygen and R_1, R_2 R_3, R_4, R_5 and the dotted line in the A ring are as previously defined. Thus Claim 28 covers loteprednol etabonate.

Claim 29

In Claim 29, which depends on Claim 14, X can be oxygen and R_1, R_2 R_3, R_4, R_5 and the dotted line in the A ring are as previously defined. Thus Claim 29 covers loteprednol etabonate.

Claim 30

In Claim 30, which depends on Claim 17, R_4 and R_5 can be hydrogen and R_1, R_2, R_3, X and the dotted line in the A ring are as previously defined. Thus Claim 30 covers loteprednol etabonate.

Claim 31

In Claim 31, which depends on Claim 18, R_4 and R_5 can be hydrogen and R_1, R_2 R_3, X and the dotted line in the A ring are as previously defined. Thus Claim 31 covers loteprednol etabonate.

Claim 32

In Claim 32, which depends on Claim 19, R_4 and R_5 can be hydrogen and R_1, R_2, R_3, X and the dotted line in the A ring are as previously defined. Thus Claim 32 covers loteprednol etabonate.

Claim 33

In Claim 33, which depends on Claim 20, R_4 and R_5 can be hydrogen and R_1, R_2, R_3, X and the dotted line in the A ring are as previously defined. Thus Claim 33 covers loteprednol etabonate.

Claim 69

In Claim 69, which depends on Claim 2, specifically recites chloromethyl-17α-ethoxycarbonyloxy-11β -hydroxyadrosta-1,4-dien-3-one-17β-carboxylate. Thus Claim 69 covers loteprednol etabonate.

Claim 88

In Claim 88, which depends on Claims 1 or 2, a pharmaceutical composition comprising an anti-inflammatory effective amount of a compound having structural formula (I) in combination with a non-toxic pharmaceutically acceptable carrier therefore, suitable for topical or other local application, wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 88 covers loteprednol etabonate.

Claim 89

In Claim 89, which depends on Claim 88, which comprises topically administering an anti-inflammatory effective amount of the composition, wherein R_1, R_2, R_4, R_5, X and the dotted line in the A ring are as previously defined. Thus Claim 89 covers loteprednol etabonate.

Claim 90

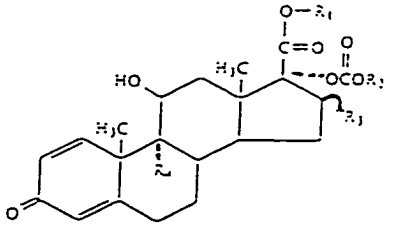
In Claim 90, which depends on Claim 88, which comprises locally administering an anti-inflammatory effective amount of the composition, wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in the A ring are previously defined. Thus Claim 90 covers loteprednol etabonate.

Claim 104

In Claim 104, which depends on Claims 1 or 2, R_3 R_4 and R_5 are hydrogen, the 1,2 linkage is unsaturated, and R_1, R_2 and X are as previously defined. Thus Claim 104 covers loteprednol etabonate.

Claim 110

Claim 110, as amended in the Request for Certificate of Correction to reflect correction of printing errors, recites compounds of the formula



wherein R_1 can be C_1-C_6 (monohalo) alkyl, R_2 can be C_1-C_6 alkyl, R_3 can be hydrogen and R_4 can be hydrogen. This structure has been corrected to show all missing dotted and wavy lines. Thus Claim 110 covers loteprednol etabonate.

Claim 111

In Claim 111, which depends on Claim 110, R1 can be chloromethyl and R_2, R_3, R_4, R_5 and X are as previously defined. Thus Claim 111 covers loteprednol etabonate.

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 USC § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

On December 1, 1988, Pharmos Corporation submitted to the Food and Drug Administration (hereinafter sometimes referred to as the "FDA") a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for P-5604 (loteprednol etabonate). A copy of each of the IND Form FDA 1571 and the IND submission letter (submitted by HGP Inc., a predecessor of Pharmos Corporation, are submitted herewith (along with a copy of a letter dated March 18, 1996 from Pharmos Corporation to the FDA appointing Bausch & Lomb Pharmaceuticals as the agent of Pharmos Corporation) as Exhibit L (IND SUBMISSION LETTER).

The IND was assigned number 32,432. The IND became effective on January 2, 1989, which is thirty days after receipt of the IND by the FDA; see Exhibit M (IND ACKNOWLEDGEMENT LETTER) attached hereto. This establishes the beginning of the "regulatory review period" under 35 USC S 156(g) (1) as of January 2, 1989.

On March 29, 1995, a new drug application (NDA 20-583), was submitted under § 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and § 314.50 of Title 21 Code of Federal Regulations for LOTEMAX™ (loteprednol etabonate) by Pharmos Corporation.

On January 31, 1997, a new drug application (NDA 20-803) was submitted under § 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and § 314.50 of Title 21 Code of Federal Regulations for ALREX™ (loteprednol etabonate) by Pharmos Corporation.

On March 7, 1997, a new drug application (NDA 20-841), was submitted under § 505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA) and § 314.50 of Title 21 Code of Federal Regulations for LOTEMAX™ (loteprednol etabonate) by Pharmos Corporation.

The data contained in NDA 20-583, NDA 20-803 and NDA 20-841 were developed by Bausch & Lomb Pharmaceuticals, Inc., and Pharmos Corporation.

A copy of the cover letter dated March 29, 1995 attached to NDA 20-583 submitted by Pharmos Corporation and the Form FDA 356h are provided herewith as Exhibit N (NDA SUBMISSION LETTER).

A copy of the cover letter dated January 31, 1997 attached to the NDA 20-803 of Pharmos Corporation and the Form FDA 356h (submitted by Bausch & Lomb Pharmaceuticals as the agent of Pharmos Corporation, pursuant to a letter from

Pharmos Corporation appointing Bausch & Lomb Pharmaceuticals as the agent of Pharmos Corporation) are provided herewith as Exhibit O (NDA SUBMISSION LETTER).

A copy of the cover letter dated March 7,1997, attached to the NDA 20-841 of Pharmos Corporation and the Form FDA 356h (submitted by Bausch & Lomb Pharmaceuticals as the agent of Pharmos Corporation, pursuant to a letter of Pharmos Corporation appointing Bausch & Lomb Pharmaceuticals as the agent of Pharmos Corporation) are provided herewith as Exhibit P (NDA SUBMISSION LETTER).

NDA 20-583 for LOTEMAX™ was approved on March 9, 1998. Attached as Exhibit E (APPROVAL LETTER) is a copy of a letter dated March 9,1998 from the FDA to Pharmos Corporation approving NDA 20-583 for LOTEMAX™ (loteprednol etabonate).

NDA 20-803 for ALREX™ was approved on March 9, 1998. Attached as Exhibit F (APPROVAL LETTER) is a copy of a letter dated March 9, 1998 from the FDA to the Pharmos Corporation approving NDA 20-803 for ALREX™ (loteprednol etabonate).

NDA 20-841 for LOTEMAX™ was approved on March 9, 1998. Attached as Exhibit G (APPROVAL LETTER) is a copy of a letter dated March 9, 1998 from the FDA to Pharmos Corporation approving NDA 20-841 for LOTEMAX™ (loteprednol etabonate).

Thus, for the purposes of determining the "regulatory review period under 35 USC § 156(g) (1), March 9, 1998 is the date of the first approval of loteprednol etabonate, which is the active ingredient in both LOTEMAX™ and ALREX™.

Summary of the Most Relevant Dates:

December 1, 1988	:	IND 32,432 for loteprednol etabonate submitted
January 2, 1989	:	IND 32,432 for loteprednol etabonate became effective
March 29, 1995	:	NDA 20-583 for LOTEMAX™ submitted
January 31, 1997	:	NDA 20-803 for ALREX™ submitted
March 7,1997	:	NDA 20-841 for LOTEMAX™ submitted
March 9, 1998	:	NDA 20-583 for LOTEMAX™, NDA 20-803 for ALREX™ and NDA 20-841 for LOTEMAX™ were approved

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10) above, an IND for loteprednol etabonate (LOTEMAX™ and ALREX™) was submitted on December 1, 1988, which became effective on January 2, 1989. The studies under the IND are summarized in the attached Exhibit Q (IND LOG). These studies were used to support NDA 20-583 submitted on March 29, 1995 by Pharmos Corporation and NDA 20-803 submitted on January 31, 1997 by the Pharmos Corporation, and NDA 20-841 submitted on March 7, 1997 by the Pharmos Corporation.

Subsequent to the submission of the aforesaid NDAs, Pharmos Corporation and Bausch & Lomb Pharmaceuticals, Inc. personnel had numerous contacts and meetings with FDA personnel with respect to the new drug application and these are summarized in the attached Exhibit R (NDA LOG)*.

Additional background information relating to preclinical and clinical studies, including approximate time frames, are summarized in the attached Exhibit S.

---

* Confidential and non-relevant material has been redacted.

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension

Under 35 USC 156 (a) and (c) (4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 USC § 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; and § 156(c) (4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding number, each of these elements is satisfied here as follows:

(1) The statutory term of U.S. Patent No. 4,996,335 expires on February 26, 2008. This Application has, therefore, been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This Application is submitted by Nicholas S. Bodor, the owner of record. This Application is submitted in accordance with 35 USC S 156(d) in that it is submitted within the sixty-day period beginning on the date, March 9, 1998, that the product received permission for marketing under the Federal Food, Drug and Cosmetic Act and contains the information required under 35 USC 156(d).

(4) As evidenced by the March 9, 1998 letters from the FDA, Exhibit E, (APPROVAL LETTER), Exhibit F (APPROVAL LETTER) and Exhibit G (APPROVAL LETTER), the product was subject to a regulatory review period under § 505(b) (1) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of LOTEMAX™ and ALREX™ (loteprednol etabonate) after regulatory review under § 505(b) (1) is the first permitted commercial marketing of loteprednol etabonate. This is confirmed by the absence of any approved new drug application under which loteprednol etabonate could be commercially marketed prior to March 9, 1998.

Statement as to Length of Extension Claimed

In Accordance with 37 CFR Section 1.775

The term of U.S. Patent No. 4,996,335 should be extended for *a* period of 1,284 days to September 2, 2011.

The period of extension is determined in accordance with 35 USC § 156 and follows the format set forth in 37 CFR § 1.775(c) and (d).

> *37* CFR § 1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 USC § 156(g) (1) (B), it is the sum
> of --
>
> (1) The number of days in the period beginning on the date an exemption under subsection (i) of Section 505 or subsection (d) of Section 507 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under Section 351 of the public Health Service Act;

The number of days between the effective date of the initial IND, January 2, 1989, and the initial submission of each of NDA 20-583, March 29, 1995, is a period of 2,277 days, and the number of days between the effective date of the initial IND, January 2, 1989, and the initial submission of NDA 20-803, January 31, 1997, is a period of 2,951 days and the number of days between the effective date of the initial IND, January 2, 1989, and the initial submission of NDA 20-841, March 7, 1997, is a period of 2,986 days and

> (2) The number of days in the period beginning on the date the application was initially submitted for the approved product under Section 351 of the Public Health Service Act, subsection (b) of Section 505 or Section 507 of the Federal Food, Drug and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of NDA 20-583, March 29, 1995, to approval of NDA 20-583, March 9, 1998, is a period of 1,076 days. The number of days between the initial submission of NDA 20-803, January 31, 1997, to approval of NDA 20-803, March 9, 1998, is a period of 402 days. The number of days between the initial submission of NDA 20-841, March 7, 1997, to approval of NDA 20-841, March 9, 1998, is a period of 367 days.

> 37 CFR S 1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by --
>
> (1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:
>
> (i) The number of days in the periods of paragraphs (c) (1) and (c) (2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on January 2, 1989, which were on or before February 26, 1991, the date the patent was issued, is a period of 785 days, 3,353 days minus 785 days equals 2,568 days, and

the number of days in the period of the NDA initial submission of NDA 20-583 on March 29, 1995, and approval on March 9, 1998, which were on or before February 26, 1991, the date the patent was issued, is a period of 0 days, the number of days in the period of the NDA initial submission of NDA 20-803 on January 31, 1997, and approval on March 9, 1998 which were on or before February 26, 1991, the date the patent was issued, is a period of 0 days, the number of days in the period of the NDA submission of NDA 20-841 on March 7, 1997, and approval on March 9, 1998, which were on or before February 26, 1991, is a period of 0 days,

2,568 days minus 0 days equals 2,568 days.

(ii) The number of days in the periods of paragraphs (c) (1) and (c) (2) of this section during which it is determined under 35 USC § 156(d) (2) (B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the Applicant did not act with due diligence is 0 days,

therefore,

2,568 days minus 0 days equals 2,568 days.

2,568 days minus 0 days equals 2,568 days.

2,568 days minus 0 days equals 2,568 days

(iii) One-half the number of days remaining in the period defined by paragraph (c) (1) of this section after that period is reduced in accordance with paragraphs (d) (1) (i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2,568 days equals 1,284 days.

Thus U.S. Patent No. 4,996,335 should be entitled to an extension of 1,284 days.

(2) By adding the number of days determined in paragraph (d) (1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 1,284 days to February 26, 2008, the original term of the patent (no terminal disclaimer was made), extends the term to September 2, 2011.

(3) By adding 14 years to the date of approval of the application under Section 351 of the Public Health Service Act, or subsection (b) of Section 505 or Section 507 of the Federal Food, Drug and Cosmetic Act;

Adding 14 years to March 9, 1998, the date of approval of the Application, results in the date of March 9, 2012.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d) (2) and (d) (3) of this Section with each other and selecting the earlier date;

The earlier date is September 2, 2011.

(5) If the original patent *was* issued after September 24,1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

(ii) By comparing the dates obtained pursuant to paragraphs (d) (4) and (d) (5) (i) of this Section with each other and selecting the earlier date;

(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and

(A) Adding 5 years to the original expiration date of the patent (February 26, 2008) gives the date of February 26, 2013.

(B) By comparing the dates obtained pursuant to paragraphs (d) (4) and (d) (5) (i) of this section with each other and selecting the earlier date;

(B) Comparing September 2, 2011 and February 26, 2013 the earlier date is September 2, 2011 and therefore the patent term should be extended to September 2, 2011.

(6) If the original patent was issued before September 24, 1984,

This is not applicable for the subject patent.

(ii) If a request was submitted for an exemption under Subsection (i) of Section 505 or Subsection (d) of Section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by --

This is not applicable for the patent.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

Applicant is unaware of any additional information material to this Application for extension.

(14) Prescribed Fee:

Please charge Deposit Account No. 02-1425 the prescribed fee for receiving and acting upon the application for extension in the amount of One Thousand One Hundred and Twenty Dollars ($1,120.00) is enclosed herewith.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Norman H. Stepno, Esq.
Burns, Doane, Swecker & Mathis LLP
P.O. Box 1404
Alexandria, VA 22313-1404

(16) A duplicate of the application papers, certified as such.

A duplicate of the application papers, certified as such, is submitted herewith. For your convenience, Patentee is attaching three additional duplicate sets of application papers.

(17) An oath or Declaration as set forth in paragraph (b) of 37 CFR 1.740. A signed declaration by the Applicant is submitted herewith in compliance with 37 CFR 1.740(a) (17).

Respectfully submitted,

DENIS A. POLYN
REG. NO. 27,152

Bausch & Lomb Inc.
One Bausch & Lomb Place
Rochester, New York 14604-2701
Telephone No. (716) 338-8417
Facsimile No. (716) 338-8706

Attorney Docket No. PO2019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Applicant of	:	Nicholas S. Bodor
U.S. Patent No.	:	4,996,335
Issue Date	:	February 26, 1991
Application Serial No.	:	807,034
Application Filing Date	:	December 9, 1985
Inventor	:	NICHOLAS S. BODOR
For	:	SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY

TRANSMITTAL OF AN APPLICATION
FOR EXTENSION OF PATENT TERM UNDER 35 USC §156

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM with attachments thereto, including Exhibits A-S, a DECLARATION, signed by the Applicant; an Associate Power of Attorney, and a Certification of Duplicate Application Copy, together with said duplicate copy, for the above-captioned patent regarding a product approved on March 9, 1998. Three additional copies of the application with attachments are also provided for the Examiner's convenience.

[X] The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-carried to the U.S. Patent and Trademark Office.

U.S. Patent No. 4,996,335

[X] Please charge the prescribed fee in the amount of $1,120.00 for the application presented to Deposit Account No. 02-1425.

In the event the actual fee differs, it is requested that the overpayment or underpayment be credited or charged to Deposit Account No. 02-1425.

Respectfully submitted,

Date: May 5, 1998

DENIS A. POLYN
REG. NO. 27,152

Denis A. Polyn, Esq.
Bausch & Lomb Inc.
One Bausch & Lomb Place
Rochester, New York 14604-2701
Telephone No. (716) 338-8417
Facsimile No. (716) 338-8706

ATTACHMENTS:

[X] Original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC §156 and attachments thereto, Exhibits A-S, with a DECLARATION and an ASSOCIATE POWER OF ATTORNEY.

[X] A certified DUPLICATE APPLICATION FOR EXTENSION OF PATENT TERM and attachments thereto, Exhibits A-S, with a DECLARATION, an ASSOCIATE POWER OF ATTORNEY and CERTIFICATION OF DUPLICATE APPLICATION COPY.

[X] Three (3) working copies of APPLICATION FOR EXTENSION OF PATENT TERM and attachments thereto, Exhibits A-S, with a DECLARATION and an ASSOCIATE POWER OF ATTORNEY.

Attorney Docket No. PO2019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Nicholas S. Bodor
U.S. Patent No.:	:	4,996,335
Issue Date	:	February 26, 1991
Application Serial No.	:	807,034
Application Filing Date	:	December 9, 1985
Inventor	:	NICHOLAS S. BODOR
For	:	SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY

DECLARATION ACCOMPANYING AN APPLICATION
FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

I, Nicholas S. Bodor, declare as follows:

1. I am an individual, residing at 6219 S. W. 93rd Avenue, Gainesville, Florida 32608.

I am the owner of United States Patent No. 4,996,335 by an assignment recorded in the United States Patent and Trademark Office on July 15, 1988, at Reel 4914, Frame 0693.

2. I have reviewed and understand the contents of the Application for Extension of Patent Term for United States Patent No. 4,996,335 submitted herewith pursuant to 35 USC 156.

3. I believe that the above-identified patent is subject to an extension pursuant to 37 CFR 1.710.

4. I believe that a 1,284 day extension of the term of the patent is fully justified under 35 USC 156 and the applicable regulations.

5. I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application for extension of patent term and United States Patent No. 4,996,335.

Wilbur S. Boutt
Name:

Gainesville, Florida
Place

April 28, 1998
Date

Patent
Attorney's Docket No.003800-006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Nicholas S. Bodor

U.S. Patent No.: 4,996,335

Issue Date: February 26, 1991

Application Serial No.: 807,034

Application Filing Date: December 9, 1985

For: SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY

ASSOCIATE POWER OF ATTORNEY

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The undersigned agent of record in the above-identified application hereby appoints Denis A. Polyn, Registration No. 27,152, as associate attorney for the limited purpose of the patent term application submitted herewith.

Inquiries and correspondence relating to this patent and application for patent term extension should continue to be directed to:

Norman H. Stepno, Esq.
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
Post Office Box 1404
Alexandria, Virginia 22313-1404

Respectfully submitted,

Burns, Doane, Swecker & Mathis

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Reg. No. 26,254

Dated: May 6, 1998

Post Office Box, 1404
Alexandria, Virginia 22313-1404
Telephone: (703) 836-6620

Patent
Attorney's Docket No.003800-006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Nicholas S. Bodor

U.S. Patent No.: 4,996,335

Issue Date: February 26, 1991

Application Serial No.: 807,034

Application Filing Date: December 9, 1985

For: SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY

CERTIFICATION OF DUPLICATE APPLICATION COPY

Box Patent Extension
Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The undersigned hereby certifies that the attached APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC § 156 for U.S. Patent 4,996,335, including Exhibits A-S, DECLARATION and ASSOCIATE POWER OF ATTORNEY are true copies of the original Application for Extension of Patent Term including, Exhibits A-S, Declaration and Power of Attorney.

Respectfully submitted,

Burns, Doane, Swecker & Mathis, L.L.P.

Dated: May 6, 1998

By: Mary Katherine Baumeister

Post Office Box, 1404
Alexandria, Virginia 22313-1404
Telephone: (703) 836-6620

Mary Katherine Baumeister
Reg. No. 26,254

LIST OF EXHIBITS

Exhibit A ..... Letter of Licensee

Exhibit B ..... Letter of Sub-Licensee

Exhibit C ..... Package Insert For Lotemax

Exhibit D..... Package Insert For Alrex

Exhibit E..... Approval Letter Lotemax (NDA 20-583)

Exhibit F ..... Approval Letter Alrex (NDA 20-803)

Exhibit G..... Approval Letter Lotemax (NDA 20-841)

Exhibit H..... Copy of Recorded Assignment

Exhibit I ..... Copy of US Patent 4,996,335

Exhibit J..... Certificate of Correction

Exhibit K..... Maintenance Fee Payment

Exhibit L ..... IND Submission Letter and authorization letter

Exhibit M ..... IND Acknowledgment Letter

Exhibit N..... NDA Submission Letter (20-583) and acknowledgment letter

Exhibit O..... NDA Submission Letter (20-803), acknowledgment letter and authorization letter

Exhibit P ..... NDA Submission Letter (20-841), acknowledgment letter and authorization letter

Exhibit Q..... IND Log

Exhibit R..... NDA Log

Exhibit S ..... Preclinical and Clinical Studies

Exhibit A

33 Wood Avenue South, Ste. 466
Iselin, New Jersey 08830
TEL 732-603-3526
FAX 732-603-3532

PHARMOS

April 13, 1998

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

Re: Application for Term Extension of
U.S. Patent No. 4,996,335

Sir:

I, Dr. Gad Riesenfeld, as President and Chief Operating Officer of Pharmos Corporation, having general authority from Pharmos Corporation to act on its behalf in patent matters, state as follows:

1. Pharmos Corporation, has a place of business 33 Wood Avenue South, Ste. 466, Iselin, New Jersey 08830. Pharmos Corporation was originally incorporated as HGP Inc. in September 1987 and the name changed to Xenon Vision Inc. in September 1989. In October 1992 all of the outstanding stock of Xenon Vision Inc. was obtained b Pharmos Corporation as part of a simultaneous merger of Pharmos Corporation, a New York Corporation, with and into Pharmatec, Inc., a Nevada Corporation. The surviving entity, which is now Pharmos Corporation, was Pharmatec, Inc., which, upon the effectiveness of the October 1992 merger, changed its name to Pharmos Corporation.

2. Pharmos Corporation is a licensee of U.S. Patent No. 4,996,335, pursuant to a license agreement with Nicholas S. Bodor, the record owner of U.S. Patent No. 4,996,335. Pharmos Corporation has granted, pursuant to a series of agreements with Bausch & Lomb Pharmaceuticals, Inc., a sub-license under U.S. Patent No. 4,996,335 to Bausch & Lomb Pharmaceuticals, Inc.

3. U.S. Patent No. 4,996,335 covers a compound known as loteprednol etabonate, the active ingredient in LOTEMAX™ and ALREX™.

4. Pharmos Corporation participated in the clinical evaluation and registration of LOTEMAX™ and ALREX™ pursuant to NDA 20-583, NDA 20-803 and NDA 20-841 which are owned by Pharmos Corporation.

5. Pharmos Corporation hereby authorizes Nicholas S. Bodor to rely on the activities of Pharmos Corporation pursuant to NDA 20-583, NDA 20-803 and NDA 20-841 to file an application under 35 U.S.C. § 156 for extension of the term of U.S. Patent No. 4,996,335.

Very truly yours,

G. Riesenfeld

Dr. Gad Riesenfeld

One Bausch & Lomb Place
Rochester NY 14604-2701
716 338 8417
Fax 716 338 6007

B

Denis A. Polyn
Staff Vice President and
Assistant General Counsel
Patent Law

BAUSCH
& LOMB
Healthcare and Optics
Worldwide

WORLDWIDE SPONSOR
1996 OLYMPIC GAMES

April 23 , 1998

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

Re: Application for Term Extension of
U.S. Patent No. 4,996,335

Sir:

I, Denis A. Polyn, as Assistant General Counsel of Bausch & Lomb Inc., having general authority from Bausch & Lomb Inc. to act on its behalf in patent matters, state as follows:

1. Bausch & Lomb Inc., specifically its wholly owned subsidiary Bausch & Lomb Pharmaceuticals, Inc., has a place of business at 8500 Hidden River Parkway, Tampa, Florida 33637.

2. Bausch & Lomb Pharmaceuticals, Inc., pursuant to a series of agreements with Pharmos Corporation, is a sub-licensee of U.S. Patent No. 4,996,335, pursuant to a license agreement with Pharmos Corporation, which is in turn a licensee of U.S. Patent 4,996,335, pursuant to a license agreement with Nicholas Bodor, the record owner of U.S. Patent No. 4,996,335.

3. U.S. Patent No. 4,996,335 covers a compound known as loteprednol etabonate, the active ingredient in LOTEMAX™ and ALREX™.

4. Bausch & Lomb Pharmaceuticals, Inc. and Bausch & Lomb Inc. participated in the clinical evaluation and registration of LOTEMAX™ and ALREX™ pursuant to NDA 20-583, NDA 20-803 and NDA 20-841 which are owned by Pharmos Corporation.

5. Bausch & Lomb Inc. hereby authorizes Nicholas S. Bodor to rely on the activities of Bausch & Lomb Inc. and Bausch & Lomb Pharmaceuticals, Inc. pursuant to NDA 20-583, NDA 20-803 and NDA 20-841 to file an application under 35 U.S.C. § 156 for extension of the term of U.S. Patent No. 4,996,335.

Very truly yours,

Denis A. Polyn
Assistant General Counsel

BAUSCH
& LOMB®

Lotemax™

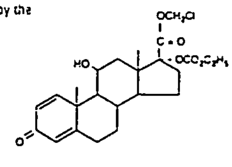
loteprednol etabonate ophthalmic suspension, 0.5%

STERILE OPHTHALMIC SUSPENSION

DESCRIPTION:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:

$C_{24}H_{31}ClO_7$



Mol. Wt. 466.96

Chemical Name:
chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each mL contains:
ACTIVE: Loteprednol Etabonate 5 mg (0.5%);
INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.
PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY:
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/ml) systemic absorption occurs with LOTEMAX.

Clinical Studies:
Post-Operative Inflammation: Placebo-controlled clinical studies demonstrated that LOTEMAX is effective for the treatment of anterior chamber inflammation as measured by cell and flare.

Giant Papillary Conjunctivitis: Placebo-controlled clinical studies demonstrated that LOTEMAX was effective in reducing the signs and symptoms of giant papillary conjunctivitis after 1 week of treatment and continuing for up to 6 weeks while on treatment.

Seasonal Allergic Conjunctivitis: A placebo-controlled clinical study demonstrated that LOTEMAX was effective in reducing the signs and symptoms of allergic conjunctivitis during peak periods of pollen exposure.

Uveitis: Controlled clinical studies of patients with uveitis demonstrated that LOTEMAX was less effective than prednisolone acetate 1%. Overall, 72% of patients treated with LOTEMAX experienced resolution of anterior chamber cell by day 28, compared to 87% of patients treated with 1% prednisolone acetate. The incidence of patients with clinically significant increases in IOP (≥10 mmHg) was 1% with LOTEMAX and 6% with prednisolone acetate 1%.

INDICATIONS AND USAGE:
LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation.

LOTEMAX is less effective than prednisolone acetate 1% in two 28-day controlled clinical studies in acute anterior uveitis, where 72% of patients treated with LOTEMAX experienced resolution of anterior chamber cells, compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (≥10 mmHg) was 1% with LOTEMAX and 6% with prednisolone acetate 1%. LOTEMAX should not be used in patients who require a more potent corticosteroid for this indication.

LOTEMAX is also indicated for the treatment of post-operative inflammation following ocular surgery.

CONTRAINDICATIONS:
LOTEMAX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. LOTEMAX is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS:
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

FL GRAPHIC ART DEPARTMENT
B&L INSERT CORE #299
INSERT SPEC SIZE: 10 3/8" x 5"
L-3002
1/C: BLACK
(FRONT)
PHARMACODE #1536

ART
QA
RA

PRECAUTIONS:
General: For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored even though it may be difficult in children and uncooperative patients (see WARNINGS).

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Information for Patients: This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX™.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (5 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (5 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:
Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2%-0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mmHg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

DOSAGE AND ADMINISTRATION:
SHAKE VIGOROUSLY BEFORE USING.

Steroid Responsive Disease Treatment: Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye(s) four times daily. During the initial treatment within the first week, the dosing may be increased, up to 1 drop every hour, if necessary. Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after two days, the patient should be re-evaluated (See PRECAUTIONS).

Post-Operative Inflammation: Apply one to two drops of LOTEMAX into the conjunctival sac of the operated eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period.

HOW SUPPLIED:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) is supplied in a plastic bottle with a controlled drop tip in the following sizes:
2.5 mL (NDC 24208-299-25) - AB29904
5 mL (NDC 24208-299-05) - AB29907
10 mL (NDC 24208-299-10) - AB29909
15 mL (NDC 24208-299-15) - AB29911

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" AND YELLOW IS NOT INTACT.

Storage: Store upright between 15°–25°C (59°–77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Rx only

Manufactured by
Bausch & Lomb Pharmaceuticals, Inc., Tampa, Florida 33637
under Agreement with Pharmos Corporation.
U.S. Patent No. 4,996,335
U.S. Patent No. 5,540,930

XO50317 (Folded)
XM10039 (Flat)
Rev. 3/98-8C

FL GRAPHIC ART DEPARTMENT
B&L INSERT CORE #299
INSERT SPEC SIZE: 10 3/8" x 5"
L-3002
1/C: BLACK
(BACK)
PHARMACODE #1536

BAUSCH & LOMB®

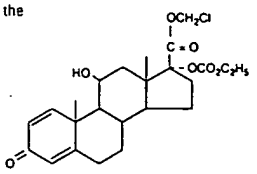
Alrex™

loteprednol etabonate ophthalmic suspension, 0.2%

STERILE OPHTHALMIC SUSPENSION

DESCRIPTION:
ALREX™ (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical Name:
chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each mL contains:
ACTIVE: Loteprednol Etabonate 2 mg (0.2%);
INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.
PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY:
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with ALREX.

Clinical Studies:
In two double-masked, placebo-controlled six-week environmental studies of 268 patients with seasonal allergic conjunctivitis, ALREX, when dosed four times per day was superior to placebo in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. ALREX provided reduction in bulbar conjunctival injection and itching, beginning approximately 2 hours after instillation of the first dose and throughout the first 14 days of treatment.

INDICATIONS AND USAGE:
ALREX Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

CONTRAINDICATIONS:
ALREX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. ALREX is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS:
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

PRECAUTIONS:
General: For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Information for Patients: This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If redness or itching becomes aggravated, the patient should be advised to consult a physician.

Patients should be advised not to wear a contact lens if their eye is red. ALREX should not be used to treat contact lens related irritation. The preservative in ALREX, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling ALREX before they insert their contact lenses.

PHARMACODE NUMBER VERIFIED

ART 3/13/98
QA 3/13/98
RA 3/13/98
PLANNING 3/13/98
MKTG/SALES 3/20/98

FL GRAPHIC ART DEPARTMENT
B&L INSERT CORE #353
INSERT SPEC SIZE: 10 3/8" x 5"
L-3002
1/C: BLACK
(FRONT)
PHARMACODE #1084

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (1500 and 750 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (15 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (15 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when ALREX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:
Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2% - 0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo. Among the smaller group of patients who were studied with ALREX, the incidence of clinically significant increases in IOP (≥10 mm Hg) was 1% (1/133) with ALREX and 1% (1/135) with placebo.

DOSAGE AND ADMINISTRATION:
SHAKE VIGOROUSLY BEFORE USING.
One drop instilled into the affected eye(s) four times daily.

HOW SUPPLIED:
ALREX™ (loteprednol etabonate ophthalmic suspension, 0.2%) is supplied in a plastic bottle with a controlled drop tip in the following sizes:
5 mL (NDC 24208-353-05) - AB35307
10 mL (NDC 24208-353-10) - AB35309

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" AND YELLOW IS NOT INTACT.

Storage: Store upright between 15°–25°C (59°–77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Rx only

Manufactured by
Bausch & Lomb Pharmaceuticals, Inc., Tampa, Florida 33637
under Agreement with Pharmos Corporation.
U.S. Patent No. 4,996,335
U.S. Patent No. 5,540,930

XO50331 (Folded)
XM10033 (Flat)
Rev. 3/98-8C

R&D Clinical Edwards Jones 3/17/98
3/18/98
3/17/98
3/17/98
3/17/98
FI ANNING

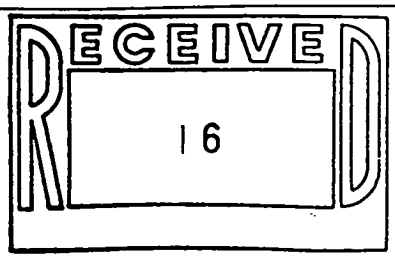
FL GRAPHIC ART DEPARTMENT
B&L INSERT CORE #353
INSERT SPEC SIZE: 10 3/8" x 5"
L-3002
1/C: BLACK
(BACK)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

E



MAR - 9 1998

NDA 20-583

Bausch & Lomb
Attention: Christine Simmons, Pharm.D
Director, Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Dr. Simmons:

Please refer to Pharmos Corporation's new drug application dated March 29, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotemax® (loteprednol etabonate ophthalmic suspension), 0.5%. Reference is also made to our not approvable letter dated April 10, 1996, and our approvable letter dated September 3, 1997.

We acknowledge receipt of your submissions dated August 20, September 18, November 11, and December 10, 11, and 16, 1997, and January 8, 14, 21, and 22, February 9 and 24, and March 6, 1998.

This new drug application provides for the use of Lotemax® for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated March 6, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on March 6, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-583. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of the Phase 4 commitments specified in your submission dated February 24, 1998. These commitments include additional stability testing on and withdrawal from the market of any loteprednol etabonate drug product in which the pH falls below 3.5. We request under 21 CFR 314.81(b)(2)(vii) that you include a status summary of each commitment in your annual report to this application. The status summary should include expected completion and submission dates and any changes in plans since the last annual report. For administrative purposes, all submissions relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lissante C. LoBianco, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

MWeintraub 3/9/98

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-803

Bausch & Lomb
Attention: Christine Simmons, Pharm.D.
Director, Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Dr. Simmons:

Please refer to Pharmos Corporation's new drug application dated January 31, 1997, received February 3, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alrex® (loteprednol etabonate ophthalmic suspension), 0.2%.

We acknowledge receipt of your submissions dated January 10, February 6, March 17, and April 15 and 30, 1997, and January 13, 14, and 16, February 9, 25, and 26, and March 3, 6, and 9, 1998.

This new drug application provides for the use of Alrex® for the temporary relief of signs and symptoms of seasonal allergic conjunctivitis.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated March 6, 1998, with the revisions identified in the submission dated March 9, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on March 6, 1998, with the March 9, 1998, revisions. Marketing the product with FPL that is not identical to this revised draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-803. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of the Phase 4 commitments specified in your submission dated February 24, 1998. These commitments include additional stability testing on and withdrawal from the market of any loteprednol etabonate drug product in which the pH falls below 3.5. We request under 21 CFR 314.81(b)(2)(vii) that you include a status summary of each commitment in your annual report to this application. The status summary should include expected completion and submission dates and any changes in plans since the last annual report. For administrative purposes, all submissions relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550 and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lissante C. LoBianco, Regulatory Health Project Manager, at (301) 827-2090.

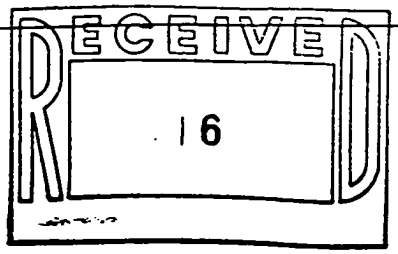
Sincerely,

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

6



Food and Drug Administration
Rockville MD 20857

NDA 20-841

Bausch & Lomb
Attention: Christine Simmons, Pharm.D
Director, Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Dr. Simmons:

Please refer to Pharmos Corporation's new drug application dated March 7, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotemax® (loteprednol etabonate ophthalmic suspension), 0.5%.

We acknowledge receipt of your submissions dated February 24, March 27, and June 16, 1997, and January 22, February 25, and March 6, 1998.

This new drug application provides for the use of Lotemax® for the treatment of post-operative inflammation following ocular surgery.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission to NDA 20-583 dated March 6, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on March 6, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-841. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lissante C. LoBianco, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

MWeintraub 3/9/98

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DS H

ASSIGNMENT

Whereas, OTSUKA PHARMACEUTICAL CO., LTD., hereinafter "assignor", a corporation organized and existing under the laws of JAPAN, is the owner of an undivided part interest in U.S. Patent Application Serial No. 807,034 filed December 9, 1985, which is a continuation of U.S. Patent Application Serial No. 626,535, filed June 29, 1984, which is a continuation of U.S. Patent Application Serial No. 416,458, filed September 15, 1982, which is a continuation-in-part of U.S. Patent Application Serial No. 265,785, filed May 21, 1981 (now abandoned), which is a continuation-in-part of U.S. Patent Application Serial No. 168,453, filed July 10, 1980 (now abandoned), in the name of Nicholas S. BODOR,

Whereas, Nicholas S. BODOR, residing at 7211 S.W. 97th Lane, Gainesville, Florida 32608, U.S.A., hereinafter "assignee", is desirous of acquiring assignor's right, title and interest, in, to and under the said application for Letters Patent and the inventions covered thereby including all foreign pricrity rights for said application.

Now, therefore, to all whom it may concern,

Be it known that for and in consideration of the sum of One Dollar ($1.00) to it in hand paid by the said assignee and other good and valuable consideration, the receipt of which is hereby acknowledged, the said assignor, has sold, assigned, transferred and set over, and does hereby sell, assign, transfer and set over to the said assignee, all of its right, title and

interest in, to and under the said inventions within the United States of America and within all countries foreign to the United States of America and in and to said patent application for Letters Patent aforesaid, and any and all continuation(s), division(s) and reissue(s) of said patent application already granted or which may be granted on said application, the same to be held and enjoyed by the same assignee, for its own use and enjoyment, and for the use and enjoyment of its successors, assigns, or other legal representatives, to the end of the term or terms for which any Letters Patent may be granted or reissued, as fully and entirely as the same would have been held and enjoyed by the said assignor, if this assignment and sale had not been made; together with all claims for damages by reason of infringement of any Letters Patent issuing on said patent application, with the right to sue for, and collect the same for its own use and behoof, and for the use and behoof of its successors, assigns or other legal representatives.

And, said assignor hereby authorizes and requests the Commissioner of Patents and Trademarks of the United States of America and any official of any country foreign to the United States of America whose duty it is to issue patents on applications for Letters Patent as aforesaid, to issue any and all Letters Patent of the United States of America or countries foreign to the United States of America or said inventions, or resulting from said patent application or from any

continuation(s), or division(s) thereof, to the said assignee, its sucessors, assigns or other legal representatives, as an assignee of an undivided part interest in the same.

And, said assignor hereby covenants and agrees that it shall at any time, upon request, execute and deliver any and all papers that may be neccesary or desirable to perfect the titles to said inventions or obtain the issuance of any Letters Patent that is or way be granted therefor, in said assignee, its successors, assigns or other legal representatives, and that if said assignee, its successors, assigns or other legal representatives desire to secure any reissue or reissues of any such Letters Patent, or that any disclaimer or disclaimers relating thereto should be filed, that assignor will, upon request, sign all papers, make all rightful oaths and do all lawful acts requisite for the application for such reissue or reissues, and the procuring thereof, or for the filing of such disclaimer or disclaimers, without further compensation or other consideration, but at the expense of said assignee, its successors, assigns or other legal representatives.

In Testimony Whereof, assignor has caused these presents to be signed by its officers thereunto duly authorized, and its corporate seal to be hereto affixed.

OTSUKA PHARMACEUTICAL CO., LTD.

(Assignor)

By A. Otsuka

Akihiko OTSUKA

Date: June 15, 1988

Title: President

United States Patent [19]

Bodor

[11] **Patent Number: 4,996,335**

[45] **Date of Patent: Feb. 26, 1991**

[54] **SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY**

[75] Inventor: Nicholas S. Bodor, 7211 SW. 97th La., Gainesville, Fla. 32608

[73] Assignee: Nicholas S. Bodor, Gainesville, Fla.

[21] Appl. No.: 807,034

[22] Filed: Dec. 9, 1985

Related U.S. Application Data

[63] Continuation of Ser. No. 626,535, Jun. 29, 1984, abandoned, which is a continuation of Ser. No. 418,458, Sep. 15, 1982, abandoned, which is a continuation-in-part of Ser. No. 265,785, May 21, 1981, abandoned, which is a continuation-in-part of Ser. No. 168,453, Jul. 10, 1980, abandoned.

[51] Int. Cl.[5] C07J 3/00; A01N 43/50

[52] U.S. Cl. 552/610; 552/611; 552/612

[58] Field of Search 260/397.1; 514/169; 552/610

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,558,675	1/1971	Sarett et al.	260/397.4
3,856,828	12/1974	Phillipps et al.	260/397.1
4,093,721	6/1978	Phillipps et al.	260/397.1
4,242,334	12/1980	Stache et al.	260/397.45
4,263,289	4/1981	Edwards	260/397.1
4,377,575	3/1983	Stache et al.	260/397.45

Primary Examiner—Stanley J. Friedman
Assistant Examiner—Theodore J. Criares
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] **ABSTRACT**

The invention provides novel soft steroidal anti-inflammatory agents, pharmaceutical compositions containing said agents, and methods of administering same to mammals in the treatment of inflammation. Preferred compounds of the invention include haloalkyl 17α-alkoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylates and the corresponding $\Delta^{1,4}$ compounds, optionally bearing 6α- and/or 9α-fluorine and 16α- or 16β-methyl substituents. Especially preferred compounds include haloalkyl 17α-alkoxycarbonyloxy-9α-fluoro-11β-hydroxy-16-methylandrosta-1,4-dien-3-one-17β-carboxylates.

113 Claims, No Drawings

SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 626,535, filed June 29, 1984, now abandoned, which is a continuation of Ser. No. 418,458, filed Sept. 18, 1982, now abandoned, which is a continuation-in-part of Ser. No. 265,785, filed May 21, 1981, now abandoned, which was a continuation-in-part of Ser. No. 168,453, filed July 10, 1980, now abandoned. The said earlier applications are expressly incorporated by reference herein in their entireties and relied upon.

TECHNICAL FIELD OF THE INVENTION

The invention relates to novel soft steroids having anti-inflammatory activity, pharmaceutical compositions containing said soft steroids, novel chemical intermediates useful in the preparation of the steroids, and methods of administering said steroids to mammals in the treatment of inflammation.

BACKGROUND ART

Successful predictions on a rational basis of the biological activity of compounds leading to new drugs are the main objective of drug designers. This has usually been achieved by considering a known bioactive molecule as the basis for structural modifications, either by the group or biofunctional moieties approach or by altering the overall physical-chemical properties of the molecule. Thus, the main aim has been to design, synthesize, and test new compounds structurally analogous to the basic bioactive molecule which have, however, improved therapeutic and/or pharmacokinetic properties. Although "vulnerable" moieties have been identified as the ones whose role is the bioinactivation or metabolic elimination of the drug after it has performed its role, little or no attention has been paid in the drug-design process to the rational design of the metabolic disposition of the drugs. This has been the case despite the fact that the toxicity of a number of bioactive molecules is due to their increased elimination half-life, stability, or other factors introduced during the design of increasing their activity. Drugs and particularly their metabolic processes contribute to the various toxic processes by formation of active metabolites. The phenomenon of metabolic activation to reactive intermediates which covalently bind to tissue macromolecules is the initial step in cell damage. It is also clear that the most toxic metabolites will not survive long enough to be excreted and identified; thus, studies of the stable metabolites may provide misleading information.

It is clear that, in order to prevent and/or reduce toxicity problems related to drugs, the metabolic disposition of the drugs should be considered at an early stage of the drug-design process. This is true particularly when one considers that the body can attack and alter chemically quite stable structures and that, even if a drug is 95% excreted unchanged, the unaccounted small portion can, and most likely will, cause toxicity.

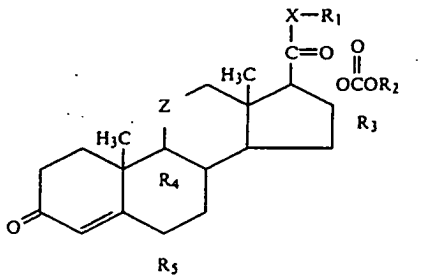
"Soft drugs" can be defined as biologically active chemical compounds (drugs) which might structurally resemble known active drugs (soft analogues) or could be entirely new types of structures, but which are all characterized by a predictable in vivo destruction (metabolism) to nontoxic moieties, after they achieve their therapeutic role. The metabolic disposition of the soft drugs takes place with a controllable rate in a predictable manner.

The present inventor has found five major classes of soft drugs. One of the most useful classes was termed the "inactive metabolite" approach which can be advantageously employed to design especially valuable "soft drugs". This approach starts with a known inactive metabolite of a drug or a drug class; followed by modifying the metabolite to resemble structurally (isosteric and/or isoelectronic) the active drug (i.e., activation); and designing the metabolism of the activated species to lead to the starting inactive metabolite after achieving the desired therapeutic role, without the formation of toxic intermediates (i.e., predictable metabolism). The "inactive metabolite" approach further allows controlling the rate of metabolism and pharmacokinetic properties by molecular manipulation in the activation stage. Also, if no useful inactive metabolite is known, one can be designed by the introduction of transporting groups in noncritical structural parts.

SUMMARY OF THE INVENTION

The present inventor has now applied his inactive metabolite approach to the case of the natural and synthetic glucocorticosteroids and has designed the soft steroidal anti-inflammatory agents of the present invention, beginning with the known inactive natural metabolites of the glucocorticosteroids. Thus, for example, in the case of hydrocortisone, one of its major, inactive metabolites, cortienic acid, i.e., 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid, has been used as a starting point and activated by the introduction of suitable non-toxic 17α- and 17β-substituents, which activated derivatives will cleave in vivo, after accomplishment of their therapeutic role, to the starting inactive metabolite and other nontoxic moieties.

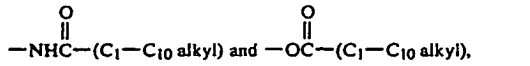
In accord with the foregoing, the present invention provides novel soft steroids having anti-inflammatory activity, said steriods having the structural formula



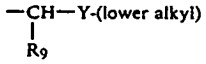
(I)

wherein:

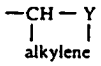
R_1 is C_1–C_{10} alkyl; C_2–C_{10} (monohydroxy or polyhydroxy)alkyl; C_1–C_{10} (monohalo or polyhalo)alkyl; or —CH_2COOR_6 wherein R_6 is unsubstituted or substituted C_1–C_{10} alkyl, C_3–C_8 cycloalkyl, C_3–C_8 cycloalkenyl or C_2–C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,



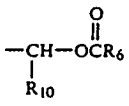
or R_6 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl-)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R_1 is $—CH_2CONR_7R_8$ wherein R_7 and R_8, which can be the same or different, are each hydrogen, lower alkyl, C_3–C_8 cycloalkyl, phenyl or benzyl, or R_7 and R_8 are combined such that $—NR_7R_8$ represents the residue of a saturated monocyclic secondary amine; or R_1 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to R_6; or R_1 is



wherein Y is —S—, —SO—, $—SO_2—$ or —O— and R_9 is hydrogen, lower alkyl or phenyl, or R_9 and the lower alkyl group adjacent to Y are combined so that R_1 is a cyclic system of the type

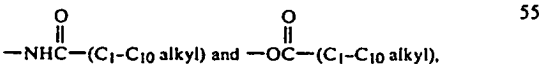


wherein Y is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms; or R_1 is



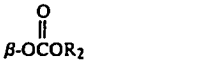
wherein R_6 is defined as hereinabove and R_{10} is hydrogen, lower alkyl, phenyl or haloalkyl;

R_2 is unsubstituted or substituted C_1–C_{10} alkyl, C_3–C_8 cycloalkyl, C_3–C_8 cycloalkenyl or C_2–C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,



or R_2 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl-)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl;

R_3 is hydrogen, α-hydroxy, β-hydroxy, α-methyl, β-methyl, $=CH_2$, or α- or



wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen, fluoro or chloro;

R_5 is hydrogen, fluoro, chloro or methyl;

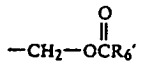
X is —O— or —S—;

Z is carbonyl or β-hydroxymethylene;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated.

A group of preferred compounds of formula (I) consists of those wherein:

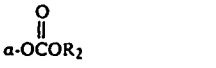
R_1 is C_1–C_6 alkyl; C_1–C_6 (monohalo or polyhalo)alkyl; $—CH_2COOR_6$ wherein R_6 is C_1–C_6 alkyl; $—CH_2—Y—(C_1$–C_6 alkyl) wherein Y is —S—, —SO—, $—SO_2—$ or —O—; or



wherein R_6' is C_1–C_6 alkyl or phenyl;

R_2 is C_1–C_6 alkyl, C_3–C_8 cycloalkyl, phenyl, benzyl or C_1–C_6 (monohalo or polyhalo)alkyl;

R_3 is hydrogen, α-hydroxy, α-methyl, β-methyl or



wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen or fluoro;

R_5 is hydrogen or fluoro;

Z is β-hydroxymethylene;

and X and the dotted line in ring A are defined as hereinabove.

The invention further provides anti-inflammatory quaternary ammonium salts of selected compounds of formula (I), as discussed in further detail below. Novel intermediates to the compounds of formula (I), e.g., the corresponding compounds wherein R_1 is hydrogen, are provided also.

The soft steroids of formula (I) and quaternary ammonium salts thereof are extremely potent local anti-inflammatory agents; however, by virtue of the fact that their facile in vivo destruction leads only to the inactive steroidal metabolite, the present compounds have far less systemic activity than the known glucocorticosteroids from whose inactive metabolites they are derived. Indeed, many of the compounds of the present invention are entirely devoid of systemic activity. Such minimal— or non-existent— systemic activity means that the compounds of the present invention can be used in the local (e.g., topical) treatment of inflammatory conditions without the serious systemic side effects which attend use of the known glucocorticosteroids.

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

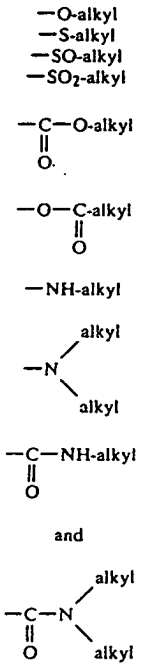
With respect to the various groups encompassed by the generic terms used here and throughout this specifi-

cation, the following definitions and explanations are applicable:

The alkyl, alkenyl and alkylene groupings can be straight or branched-chain groups containing the aforementioned number of carbon atoms. Likewise, the alkyl portions of the alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkanoyloxy, haloalkyl, monoalkylamino, dialkylamino, monoalkylcarbamoyl and dialkylcarbamoyl groupings each can be straight or branched-chain. The term "lower" used in conjunction with any of those groupings or in conjunction with "alkyl" is intended to indicate that each alkyl portion therein can contain 1 to 8 carbon atoms.

Specific examples of alkyl radicals encompassed by formula (I), whether as specific values for R_1 or R_2, or as a portion of a R_1, R_2, or R_3 group, include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl and their branched-chain isomers, as well as their straight and branched-chain higher homologues in the instances where "alkyl" can contain more than 8 carbon atoms. The alkenyl radicals can be exemplified by vinyl, propenyl and butenyl. Illustrative of the cycloalkyl and cycloalkenyl radicals are cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl. The alkylene moieties are typified by timethylene, tetramethylene and the like.

The alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonyl, alkanoyloxy, monoalkylamino, dialkylamino, monoalkylcarbamoyl and dialkylcarbamoyl



respectively, wherein alkyl is as hereinbefore defined and exemplified.

With respect to the structural variables encompassed by the group of preferred compounds of formula (I) identified hereinabove, the term "C_1-C_6 alkyl" is used to refer to a straight or branched-chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl and the like. In addition, the term "C_1-C_6 (monohalo or polyhalo)alkyl" is used to refer to a straight or branched-chain alkyl group having 1 to 6 carbon atoms substituted with from 1 to 3 halogen atoms, the term "halogen" as used herein including a chlorine atom, a bromine atom, an iodine atom or a fluorine atom. Specific examples of the contemplated monohaloalkyl and polyhaloalkyl groups include chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1-chloroethyl, 2-chloroethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 1,2-dichloroethyl, 1-chloropropyl, 3-chloropropyl, 1-chlorobutyl, 1-chloropentyl, 1-chlorohexyl, 4-chlorobutyl and the like. Also, the term "C_3-C_8 cycloalkyl" is used to refer to a cycloalkyl radical having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

When R_1 in formula (I) is $—CH_2CONR_7R_8$ wherein $—NR_7R_8$ represents the residue of a saturated monocyclic secondary amine, such monocycles preferably have 5 to 7 ring atoms optionally containing another hetero atom (—O—, —S— or —N—) in addition to the indicated nitrogen atom, and optionally bear one or more substituents such as phenyl, benzyl and methyl. Illustrative of residues of saturated monocyclic secondary amines which are encompassed by the $—NR_7R_8$ term are morpholino, 1-pyrrolidinyl, 4-benzyl-1-piperazinyl, perhydro-1,2,4-oxathiazin-4-yl, 1- or 4-piperazinyl, 4-methyl-1-piperazinyl, piperidino, hexamethyleneimino, 4-phenylpiperidino, 2-methyl-1-pyrazolidinyl, 1- or 2-pyrazolidinyl, 3-methyl-1-imidazolidinyl, 1-or 3-imidazolidinyl, 4-benzylpiperidino and 4-phenyl-1-piperazinyl.

Selected compounds of formula (I), i.e. compounds wherein R_1 is α-haloalkyl, readily form the corresponding soft quaternary ammonium salts which are likewise useful as soft anti-inflammatory agents. Thus, for example, the selected haloalkyl derivative of formula (I) can simply be reacted with a tertiary amine

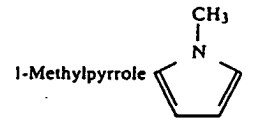
or an unsaturated amine

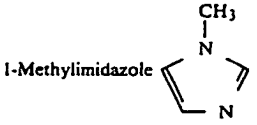
to afford the corresponding quaternary ammonium salt. The reactants are generally used in approximately equimolecular proportions and the reaction is conducted in the presence of an inert solvent (e.g., ether, acetonitrile, CH_2Cl_2 or the like), at a temperature of from room temperature to the reflux temperature of the solvent, for approximately 2 to 24 hours. Alternatively, the reaction can be conducted in the absence of a solvent by mixing the two reactants together and maintaining them at room temperature or between 20° to 70° C. for 2 to 24 hours. In either case, the crystalline salt formed can be purified by crystallization from an ether-ethanol mixture, or the like.

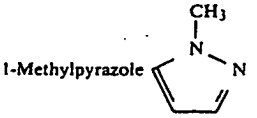
The expression "unsaturated amine" used above denotes N-heterocyclic unsaturated systems having 3 to 10 members in the ring, and substituted derivatives thereof, where the unsaturation corresponds to the maximum number of non-cumulative double bonds, provided that the nitrogen atom contains no hydrogen

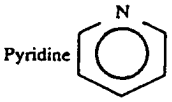
atom as a substituent. The following examples will sufficiently illustrate the scope of the defined term:

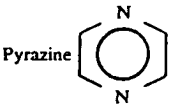

1-Methylazirine

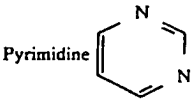

1-Methylpyrrole

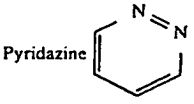

1-Methylimidazole

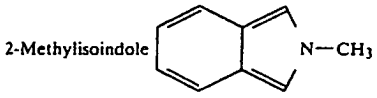

1-Methylpyrazole

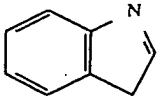

Pyridine

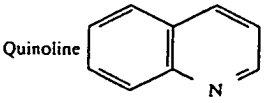

Pyrazine

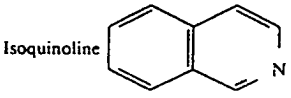

Pyrimidine

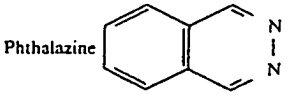

Pyridazine


2-Methylisoindole

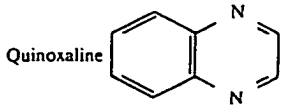

3H-indole

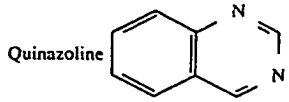

Quinoline

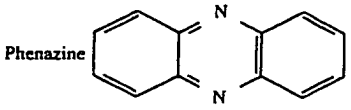

Isoquinoline

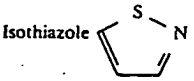

Phthalazine

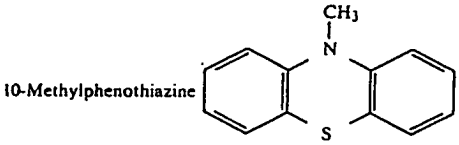
-continued

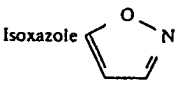

Quinoxaline

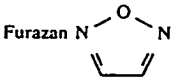

Quinazoline


Phenazine


Isothiazole


10-Methylphenothiazine


Isoxazole


Furazan

Substituted derivatives of the unsaturated amines include groups as shown above containing one or more alkyl, —COO(alkyl) or —OCO(alkyl) substituents.

With respect to the expression "tertiary amine", this expression denotes amines wherein the nitrogen atom has no hydrogen atoms attached thereto and which are not among the N-heterocyclic unsaturated systems encompassed by the expression "unsaturated amine" as defined above. Typically, the term "tertiary amine" includes trialkylamines, wherein the alkyl groups, which can be the same or different, each preferably contain 1 to 8 carbon atoms; trialkoxyamines wherein the alkoxy portions each contain 1 to 8 carbon atoms; tertiary saturated cyclic amines such as quinuclidine or substituted quinuclidine (e.g., 3-acetoxyquinuclidine); and N-substituted derivatives of secondary saturated cyclic amines [e.g., an N-substituted derivative or morpholine, pyrrolidine, imidazolidine, pyrazolidine, piperidine or piperazine, wherein the N-substituent can be a group such as (C_1–C_8) alkyl], optionally containing additional substituents such as methyl.

Preferred quaternary ammonium salts include those derived from 1,2-dimethylpyrrolidine, 3-acetoxyquinuclidine, 1-methylpyrrolidine, triethylamine and N-methylimidazole. Especially preferred are the quaternary ammonium salts derived from the reaction of the aforesaid amines with compounds of formula (I) wherein Z is β-hydroxymethylene and R_1 is chloromethyl, most especially when R_2 is lower alkyl.

While all of the compounds encompassed by formula (I) above essentially satisfy the objectives of the present invention, nevertheless certain groups of compounds remain preferred. A "first" group of preferred com-

pounds of formula (I) has been set forth in the Summary of the Invention hereinabove.

Another preferred group of compounds consists of the compounds of formula (I) wherein Z, X, R_1 and R_2 are defined as hereinabove, and the remainder of the structural variations are identical to those of hydrocortisone (i.e. R_3, R_4 and R_5 are each a hydrogen atom and the 1,2-linkage is saturated) or of prednisolone (i.e., R_3, R_4 and R_5 are each a hydrogne atom and the 1,2-linkage is unsaturated), most especially when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove.

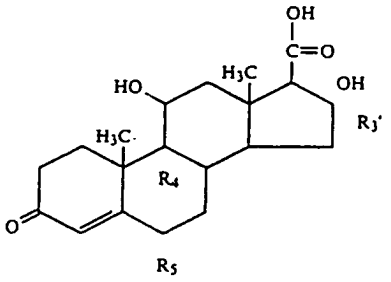
Another preferred group of compounds consists of the 6α- and/or 9α-fluoro and 16α- or 16β-methyl congeners of the compounds indicated in the preceding paragraph. Within this group, the compounds wherein Z, X, R_1 and R_2 are defined as hereinabove and the remaining structural variables are identical to those of fludrocortisone, betamethasone and dexamethasone are particularly preferred, most especially when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Other compounds of particular interest within this group are those wherein Z, X, R_1 and R_2 are defined as hereinabove and the remaining structural variables are identical to those of triamcinolone, flumethasone, fluprednisolone or paramethasone, particularly when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Yet other interesting compounds are those wherein Z, X, R_1 and R_2 are defined as hereinabove, R_3 is

and the remaining structural variables are identical to those of triamcinolone, particularly when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove.

In each of the groups of compounds indicated in the three preceding paragraphs, the compounds wherein X is oxygen are particularly preferred. Most especially preferred are the compounds encompassed by the groups indicated above wherein Z is β-hydroxymethylene, wherein X is oxygen, wherein R_2 is C_1-C_6 alkyl (particularly methyl, ethyl, propyl or isopropyl), and wherein R_1 is C_1-C_6 alkyl, C_1-C_6 (monohalo)alkyl (particularly chloromethyl) or —CH_2—Y—(C_1-C_6 alkyl) wherein Y is defined as hereinabove (particularly when the C_1-C_6 alkyl group is methyl).

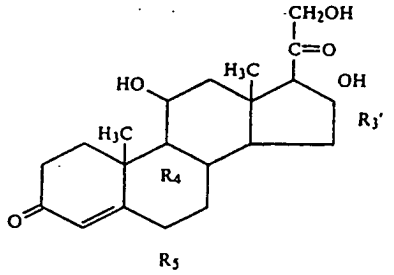
The compounds of formula (I) can generally be prepared by known methods, the method of choice being dependent on the identity of the various substituents in the desired final product.

One generally useful method for the preparation of the compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen utilizes steroidal starting materials of the formula

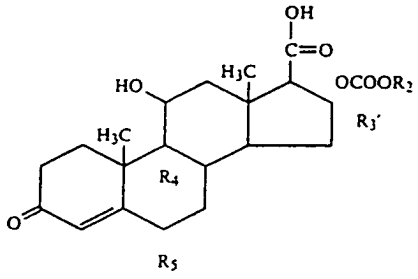


(II)

wherein R_4, R_5 and the dotted line in ring A are defined as before and R_3' is hydrogen, α-methyl, β-methyl, α-OH, β-OH or $=CH_2$ (and which can be conveniently prepared by treatment of the corresponding 21-hydroxypregnenolones of the formula



wherein R_4, R_5, R_3' and the dotted line in ring A are defined as above with $NaIO_4$ in a suitable organic solvent at room or elevated temperature.) According to this process of the invention, a starting material of formula (II) is reacted with R_2OCOCl or R_2OCOBr (formed by reacting R_2OH with $COCl_2$ or $COBr_2$, wherein R_2 is defined as above), under anhydrous conditions, in an appropriate inert organic solvent such as dichloromethane, chloroform or tetrahydrofuran, preferably in the presence of a suitable acid acceptor (e.g., triethylamine, pyridine, calcium carbonate or other appropriate base). Time and temperature are not critical factors; however, the reaction is conveniently carried out at a temperature between 0° C. and room temperature, for about 1 to 6 hours. The resultant novel 17β-carboxylic acid 17α-carbonate has the formula



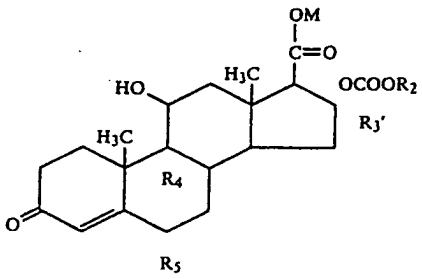
(III)

wherein R_2, R_4, R_5 and the dotted line in the A ring are defined as above and R_3'' is H, α-CH_3, β-CH_3, α-$OCOOR_2$, β-$OCOOR_2$ or $=CH_2$. When R_3' in the starting material of formula (II) is α-OH or β-OH, sufficient R_2OCOCl or R_2OCOBr is generally employed to ensure formation of the carbonate grouping at the 16-position as well as at the 17-position [i.e., when R_3' in

formula (II) is OH, R_3'' in the resultant intermediate of formula (III) is α- or β-$OCOOR_2$].

Sometimes, when a compound of formula (I) wherein R_2 contains a sulfinyl or sulfonyl grouping is desired, such a grouping is not introduced via the R_2OCOCl/-R_2OCOBr reaction, but is prepared from the corresponding thio-containing R_2 derivative at a later stage in the synthetic scheme, as will be discussed in more detail below.

After the above-described introduction of the 17α-substituent, the resultant novel intermediate of formula (III) is converted to its corresponding metal salt of the formula



(IV)

wherein R_2, R_3'', R_4, R_5 and the dotted line in the ring A are defined as above, and M is a suitable metal, e.g. alkali metal (such as sodium or potassium), alkaline earth metal/2, or thallium or NH_4^+. The novel salt of formula (IV) is typically formed by reacting the steroid of formula (III) with a hydroxide (MOH) or alkoxide (MOR) in a appropriate organic solvent, such as ethyl ether or tetrahydrofuran, at a temperature of 0° C. to room temperature, for 0.5 to 4 hours. Then, the salt of formula (IV) is reacted with a compound of the formula R_1-W wherein R_1 is defined as hereinabove and W is halogen, to afford the desired final product of formula (I). This step of the reaction sequence can be conveniently conducted at room temperature for about 1 to 24 hours, or at the boiling of the solvent (i.e. acetonitrile, THF, etc.) When it is desired to introduce a halo-substituted R_1 grouping into the steroid, e.g., when a compound of formula (I) wherein R_1 is chloromethyl is desired, it has been found that the reaction proceeds well using hexamethylphosphoramide as the solvent at lower temperatures (0°-10° C.) and employing a R_1-W reactant wherein W is iodine (e.g., iodochloromethane). When a non-halogen containing R_1 grouping is desired (e.g., R_1=alkyl or $-CH_2COOR_6$ where R_6 is alkyl, etc.), no such restrictions need by placed on the R_1-W reactant or on the solvent; thus, W can be any halogen, preferably chloro or bromo, and the usual organic solvents such as dimethylformamide, dichlormethane, acetonitrile, tetrahydrofuran or chloroform can, if desired, be used instead of hexamethylphosphoramide. When a compound of formula (I) wherein R_1 contains a sulfinyl or sulfonyl grouping is desired, such a grouping is not generally introduced via the R_1-W reaction, but is subsequently prepared from the corresponding thio steroid, as described below.

The compounds of formula (I) wherein R_1 (or R_2) is a sulfinyl- or sulfonyl-containing grouping can be prepared by oxidation of the corresponding thio steroids. Thus, for example, a compound of formula (I) wherein R_1 is

$$-\underset{\underset{R_9}{|}}{CH}-S\text{-(lower alkyl)}$$

[wherein R_9 is H, lower alkyl, or combined with the lower alkyl group adjacent to S to form a cyclic system, as described hereinabove] can be reacted wtih 1 equivalent of m-chloroperoxybenzoic acid at 0°-25° C. for 1 to 24 hours, in a suitable solvent such as chloroform, to afford the corresponding compound of formula (I) wherein R_1 is

$$-\underset{\underset{R_9}{|}}{CH}-SO\text{-(lower alkyl)},$$

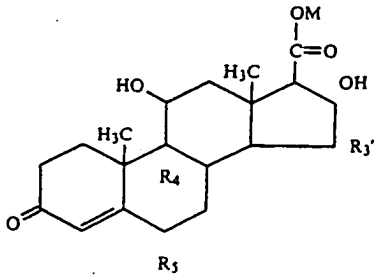
or with 2 equivalents of m-chloroperoxybenzoic acid to afford the corresponding compound of formula (I) wherein R_1 is

$$-\underset{\underset{R_9}{|}}{CH}-SO_2\text{-(lower alkyl)}.$$

This type of reaction can also be utililzed to prepare compounds of formula (I) wherein R_1 is $-CH_2COOR_6$ wherein R_6 is substituted alkyl, cycloalkyl, cycloalkenyl, alkenyl, phenyl, or benzyl, wherein the substituent is lower alkylsulfinyl or lower alkylsulfonyl, from the corresponding lower alkylthio-substituted formula (I) steroids; to prepare compounds of formula (I) wherein R_1 is lower alkylsulfinyl- or alkylsulfonyl-substituted phenyl or benzyl from the corresponding lower alkylthio-substituted formula (I) steroids; and to prepare compounds of formula (I) wherein R_2 is substituted alkyl, cycloalkyl, cycloalkenyl, alkenyl, phenyl or benzyl wherein the substituent is lower alkylsulfinyl or lower alkylsulfonyl, from the corresponding lower alkylthio-substituted formula (I) steroids.

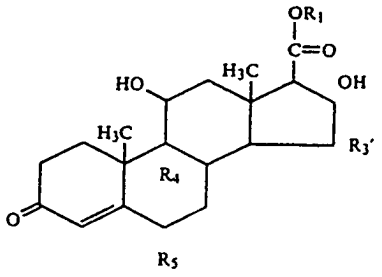
When the compounds of formula (I) wherein R_3 is α- or β-hydroxy are desired, same can be prepared by partial acid hydrolysis of the corresponding compounds of formula (I) wherein R_3 is α- or β-$OCOOR_2$, in a suitable solvent medium. Use of a mild reagent, e.g., oxalic acid in methanol, is desirable. Alternatively, hydrolysis of the 16-carbonate to the 16-hydroxy compound could be carried out at an earlier stage in any synthetic scheme described herein after the introduction of the 16,17-carbonate groupings, e.g., selective hydrolysis of an intermediate of formula (III) having 16 and 17 carbonate groupings to the corresponding 16-hydroxy 17-carbonate, followed by conversion to the corresponding compound of formula (I) as described supra.

Another process for the preparation of the compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen utilizes the same 17α-hydroxy-17β-carboxylic acid starting materials of formula (II) as are employed in the synthetic scheme described supra, but involves formation of the 17β-$COOR_1$ grouping prior to, rather than after, introduction of the 17α-$OCOOR_2$ substituent. Essentially, the same non-steroidal reactants, reaction conditions, etc., as described above are used for the introduction of each group. Thus, the starting material of formula (II) is first reacted with MOH or MOR to form the corresponding intermediate of the formula



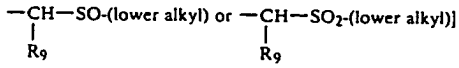
(V)

wherein R_3', R_4, R_5 and M and the dotted line in ring A are defined as above, which is then reacted with R_1W wherein R_1 and W are defined as above, to afford the corresponding 17β-carboxylate of the formula



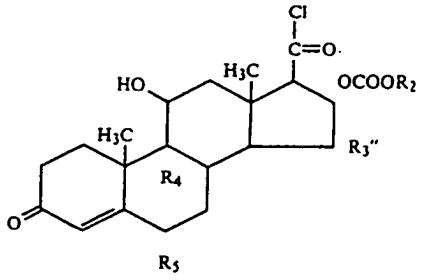
(VI)

wherein R_1, R_3', R_4, R_5 and the dotted line in ring A are defined as above, which is in turn reacted with R_2O-COCl or R_2OCOBr wherein R_2 is defined as above, to afford the corresponding 17α-carbonate of formula (I). The various parameters of the process of converting (II) to (V) are the same as those discussed in detail above with respect to the conversion of (III) to (IV). Likewise, the process parameters for converting (V) to (VI) parallel those detailed above with respect to converting (IV) to (I). Similarly, the process parameters for converting (VI) to (I) are basically the same as those given above for the conversion of (II) to (III). Thus, again, when the starting material contains a 16-hydroxy group, the 16,17-dicarbonate of formula (I) will be formed which can then be selectively hydrolyzed, if desired, to the corresponding 16-hydroxy-17-carbonate of formula (I). And, again, the compounds of formula (I) in which R_1 or R_2 is a sulfinyl- or sulfonyl-containing grouping can be conveniently prepared by oxidation of the corresponding thio-containing compounds of formula (I) as detailed hereinabove. Alternatively, the compounds of formula (I) wherein R_1 is



can be prepared by oxidation, preferably with m-chloroperoxybenzoic acid, of the corresponding compounds of formula (VI) in which R_1 is a thio-containing group, followed by introduction of the 17α-$OCOOR_2$ substituent to the resultant sulfinyl or sulfonyl compound.

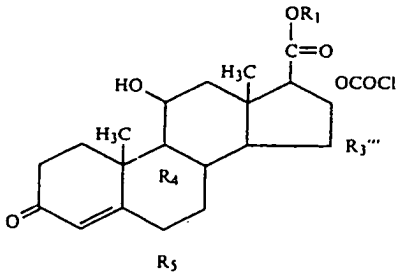
Another possible process for the preparation of the compounds of the present invention, which can be used to prepare compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen or sulfur, utilizes the 17β-carboxylic acid 17α-carbonate intermediates of formula (III) above. According to this process, an intermediate of formula (III) is successively treated, first with a mild acyl chloride forming agent, e.g. such as diethylchlorophosphate or oxalyl chloride, to form the corresponding novel acid chloride of the formula



(VIII)

wherein R_2, R_3'', R_4, R_5 and the dotted line in ring A are defined as above, and then with R_1XM' wherein R_1 and X are defined as before, and M' is hydrogen or M (M is defined as above), in an inert solvent (e.g., $CHCl_3$, THF, acetonitrile or DMF), at a temperature between about 0° C. and the boiling point of the solvent, for 1 to 6 hours, to afford the corresponding compound of formula (I). When using a compound of the formula R_1XM' wherein M' is hydrogen, an acid scavenger such as triethylamine is preferably present in the reaction system. The two steps of this process can be very conveniently run in the same solvent, without isolating the acid chloride of formula (VIII) formed in the first step. This process is of particular value when a compound of formula (I) wherein X is S is desired.

Yet another desirable process for the preparation of the compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen utilizes the 17α-hydroxy-17β-carboxylates of formula (VI) above. According to this process, an intermediate of formula (VI) is reacted with phosgene, in a suitable organic solvent (e.g., toluene, benzene, CH_2Cl_2 or acetonitrile) at a low temperature (−20° C. to room temperature, e.g., 0° C.), for about 2 hours (or until the reaction is complete). Evaporation to remove solvent and excess phuosgene affords the desired novel 17α-chlorocarbonyloxy-17β-carboxylate intermediate of the formula

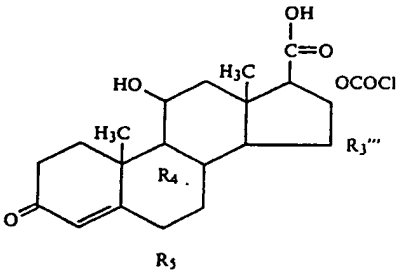


(VII)

wherein R_1, R_4, R_5 and the dotted line in ring A are defined as above, R_3''' is hdyrogen, α-methyl, β-methyl, α-OCOCl, β-OCOCl or $=CH_2$. When R_3' in the starting material of formula (VI) is hydroxy, sufficient phosgene is generally employed to ensure formation of the chlorocarbonyloxy grouping at the 16-position as well as the 17-position [i.e., when R_3' in formula (VI) is α-OH or β-OH, R_3''' in the resultant intermediate of formula (VII) is α- or β-OCOCl]. The intermediate of formula (VII) is then reacted with a compound of the formula R_2OM' wherein R_2 and M' are defined as

above, in an inert solvent, preferably in the presence of an acid scavenger (e.g. triethylamine), to afford the corresponding compound of formula (I). When R_2OM' is an alcohol of the formula R_2OH, the reaction is conducted under the same conditions as in the reaction for conversion of compound (II) to compound (III). On the other hand, if a compound of the formula R_2OM is employed as R_2OM', the reaction conditions are described as above for conversion of compound (VIII) to compound (I). When R_3''' in th formula (VII) is OCOCl, sufficient R_2OM' is generally utilized to ensure conversion of both the 16- and 17α-substituents to $OCOOR_2$ groupings in the final product. And, again, the 16-hydroxy and the sulfinyl- and sulfonyl- containing compounds of formula (I) are most conveniently formed as a final step in the synthetic scheme.

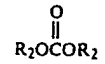
As a variation of the process described immediately above, a steroidal 17α-hydroxy-17β-carboxylic acid starting material of formula (II) can be reacted with phosgene as described above, to afford the 17α-chlorocarbonyloxy-17β-carboxylic acid intermediate of the formula



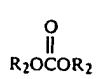
(X)

wherein R_3''', R_4, R_5 and the dotted line in ring A are defined as above, which can then be reacted with R_2OM' as described supra, to afford the corresponding compound of formula, (III) above. The novel intermediate can then be converted to a corresponding compound of formula (I) as described supra. Once again, the 16-hydroxy and the sulfinyl and sulfonyl derivatives are best prepared as a final step.

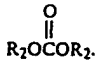
Still another process for the preparation of the compounds of formula (I) wherein Z is β-hydroxymethylene and X is oxygen utilizes the 17α-hydroxy-17β-carboxylates of formula (VI) above. In accord with this method, an intermediate of formula (VI) is reacted with an excess amount of a carbonate of the formula



(which can be conveniently prepared by reacting phosgene with 2 equivalents of R_2OH) in the presence of an acid catalyst, to afford the corresponding compound of formula (I). Depending on the nature of the R_2 grouping, the



reactant can also act as the solvent at the boiling point of the carbonate reactant, or at the boiling point of the corresponding R_2OH (which can conveniently be removed in this way from the reaction mixture, driving the reaction to completion), or the reactants can be combined in an appropriate inert organic solvent (e.g., an aromatic such as benzene or toluene, or a halogenated hydrocarbon such as dichloromethane or chloroform). And, again, the 16-hydroxy and the sulfinyl and sulfonyl compounds of formula (I) can conveniently be prepared as a final step in the process, although the intermediate of formula (VI) in which R_1 contains a sulfur atom could be first oxidized, and the resultant sulfinyl or sulfonyl compound of formula (VI) then reacted with

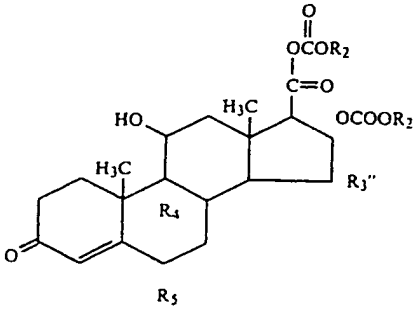


Other procedures for the preparation of selected compounds of formula (I) will be apparent to those skilled in the art. By way of example, a compound of formula (I) wherein R_1 or R_2 is halo-substituted can be subjected to a halogen exchange reaction in order to replace the halogen with a different halogen according to the order of reactivity Cl<Br<I. For example, reacting a chloroalkyl 17β-carboxylate of formula (I) with an alkali metal iodide, e.g., sodium iodide, will afford the corresponding iodoalkyl 17β-carboxylate. Similarly, a bromide salt (e.g., lithium bromide) can be reacted with a chloroalkyl 17β-carboxylate to give the corresponding bromoalkyl 17β-carboxylate. A suitable solvent for either reaction may be selected from the group consisting of hexamethylphosphoramide, acetone, ethanol, methyl ethyl ketone, dimethylacetamide, dimethylformamide and acetonitrile.

In like manner, a halogen exchange reaction based on relative solubilities can be used to convert a chloroalkyl 17β-carboxylate or an iodoalkyl 17β-carboxylate of formula (I) to the corresponding fluoroalkyl derivative. Silver fluoride can be employed in this reaction, which is conducted in a suitable organic solvent (e.g., aceytonitrile), and which is especially useful in the preparation of the compounds in which R_1 is fluoromethyl or fluoroethyl.

The 21-hydroxypregnenolones from which the steroidal starting materials of formula (II) are prepared can be obtained commercially or prepared by known methods. Likewise, the non-steroidal starting materials used in the various processes discussed above are commercially available or can be prepared by known chemical procedures.

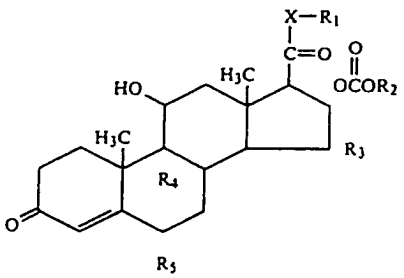
Also, a starting material of formula (II) above can be reacted with a compound of the formula R_2OCOCl or R_2OCOBr wherein R_2 is as defined above, to afford an intermediate of the formula



(XI)

wherein R_2, R_3'', R_4, R_5 and the dotted line in ring A are defined as above, which can be converted to the corresponding intermediate of formula (III) above by partial hydrolysis, with or without isolation of the compound of formula (XI). This reaction of a starting material of formula (II) with R_2OCOCl or R_2OCOBr can be carried out under the same conditions as the reaction of a compound of formula (II) with R_2OCOCl or R_2OCOBr as described hereinabove, except that R_2OCOCl or R_2OCOBr is used in an amount of 2 moles or more to one mole of the compound of the formula (II). The partial hydrolysis of the resultant compound of the formula (XI) can be carried out in an inert solvent in the presence of a catalyst. Examples of suitable catalysts include tertiary alkyl amines such as triethylamine, trimethylamine or the like; aromatic amines such as pyridine, 4,4-dimethylaminopyridine, quinoline or the like; secondary alkyl amines such as diethylamine, dimethylamine or the like; and inorganic bases such as sodium hydroxide, potassium hydroxide, potassium bicarbonate, or the like. Preferably, pyridine and potassium bicarbonate are employed. Examples of suitable inert solvents for use in the hydrolysis include water; lower alcohols such as ethanol, methanol or the like; ethers suchy as dimethyl ether, diethyl ether, dimethoxyethane, dioxane, tetrahydrofuran, or the like; halogenated hydrocarbons such as dichloromethane, chloroform or the like; tertiary amines such as pyridine, triethylamine or the like; or a mixture of two or more of the solvents mentioned above. The reaction is usually carried out a temperature of from about 0° to 100° C., preferably at room temperature to 50° C., for 1 to 48 hours, preferably for 2 to 5 hours.

In yet another aspect, the present invention provides novel compounds of the formula



(IX)

wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in ring A are as defined with respect to formula (I) above. The 11-keto compounds of formula (IX) can be prepared by the procedures described hereinabove for the preparation of the corresponding 11β-hydroxy compounds of formula (I). Thus, a starting material corresponding to formula (II) but having an 11-keto group is reacted with R_2OCOCl or R_2OCOBr, to afford the corresponding novel intermediate corresponding to formula (III) but having an 11-keto group; that intermediate is then converted to its metal salt, which corresponds to formula (IV) except for the presence of an 11-keto instead of an 11β-hydroxy group; and the metal salt is then reacted with R_1W to afford the corresponding compound of formula (IX). All reaction conditions are as previously described with respect to the corresponding processes for preparing the corresponding compounds of formula (I). Also, the preparation of the compounds of formula (IX) wherein R_1 is a sulfinyl- or sulfonyl- containing grouping or wherein R_3 is hydroxy generally proceeds as a final step in the synthetic scheme in a manner analogous to that used for the corresponding compounds of formula (I). Further, all of the above-described alternative processes for the preparation of the compounds of formula (I) are equally applicable to the preparation of the compounds of formula (IX) by simply substituting the 11-oxo starting material for the corresponding 11β-hydroxy steroids used therein, e.g., replacing the 11-hydroxy group in formulas (V), (VI), (VII), (VIII), (X) and (XI) with an 11-oxo group and otherewise proceeding as described hereinabove for the reactions (II)→(V)→(VI)→(I); (III)→(VIII)→(I); (VI)→(VII)→(I); (II)→(X)→(I); (VI)→(I), etc.

Also, the compounds of formula (IX) can be prepared by reacting the corresponding compounds of formula (I) with an oxidizing agent. The oxidation of a compound of formula (I) in order to convert it into the corresponding compound of formula (IX) is usually carried out by using an oxidizing agent in an appropriate solvent. The solvent may be any conventional solvent, for example, water, and organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid), an alcohol (e.g. methanol, ethanol), a halogenated hydrocarbon (e.g. chloroform, dichloromethane), or the like. This oxidizing agent may also be any conventional agent which is effective for oxidizing a hydroxy group to a carbonyl group, for example, pyridinium chlorochromate, chromium trioxide in pyridine, hydrogen peroxide, dichromic acid, dichromates (e.g. sodium dichromate, potassium dichromate), permanganic acid, permanganates (e.g. sodium permanganate, potassium permanganate), or the like. The oxidizing agent is usually used in an amount of 1 mole or more, preferably 1 to 3 mole, per mole of the compound of formula (I). The reaction is usually carried out at a temperature of 0° to 40° C., preferably at around room temperature, for about 6 to 30 hours.

The novel compounds of formula (IX) are useful as soft steroidal anti-inflammatory agents and also in vivo or in vitro precursors of the corresponding 11β-hydroxy compounds. Thus, the compounds of formula (IX) can be reduced in vitro to afford the corresponding compounds of formula (I), using a reducing agent known to be capable of reducing the 11-oxo group to an a 11β-hydroxy group without modifying the remainder of the steroidal starting material. Typically, microbiological reduction is advantageous for carrying out the desired conversion, although chemical reduction also is possible. Further, the compounds of formula (IX) may be formulated into appropriate dosage forms (e.g., retention enemas) for the treatment of conditions such as ulcerative colitis. In such dosage forms, it is thought that the compounds of formula (IX) are microbiologically reduced by bacteria in the body (e.g. in the colon) to the highly active 11β-hydroxy steroids, which elicit the desired anti-inflammatory response.

The preferred compounds of formula (IX) are those which are precursors of the preferred compounds of formula (I) wherein Z is β-hydroxymethylene, namely corresponding 11-keto compounds of formula (IX). As especially preferred group of compounds of formula (IX) consists of those wherein X, R_1 and R_2 are defined as above with respect to formula (I) and the remaining structural variations are identical to those of cortisone (i.e. R_3, R_4 and R_5 are each a hydrogen atom and the 1,2-linkage is saturated), of prednisone (i.e. R_3, R_4 and R_5 are each hydrogen and the 1,2-linkage is unsaturated), or of the 6α- and/or 9α-fluoro and the 16α- or

16β-methyl congeners thereof, particularly when R_1 and R_2 are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Most especially preferred of these derivatives are those wherein X is oxygen, R_2 is C_1-C_6 alkyl and R_1 is C_1-C_6 alkyl, C_1-C_6 (monohalo)alkyl [particularly chloromethyl] or —CH_2—Y—(C_1-C_6 alkyl) [particularly —CH_2—Y—CH_3].

The results of various activity studies of representative species of the invention, discussed in detail below, clearly indicate the potent anti-inflammatory activity and the minimal systemic activity/toxicity of the soft steroids of formula (I). In view of this desirable separation of local and systemic activities, the compounds of the invention can be used in the treatment of topical or other localized inflammatory conditions without causing the serious systemic side effects typically exhibited by the known natural and synthetic glucocorticosteroids such as cortisone, hydrocortisone, hydrocortisone 17α-butyrate, betamethasone 17-valerate, triamcinolone, betamethasone dipropionate and the like.

THYMUS INVOLUTION TEST

The test animals were female Sprague/Dawley rats weighing approximately 40–45 grams each. One side of each ear of each rat was treated with a total of 25 microliters of a solution (ethanol/isopropyl myristate or acetone/isopropyl myristate, 90/10) containing the amount of test compound indicated below. Animals which were treated identically, save for omission of the test compound, served as controls. After 24 hours, all rats were sacrificed and weighed, and their thymi were removed and weighed. The results are tabulated in Table I below, the weights of the thymi being expressed as mg/100 g of rat.

TABLE I

Effect of topically administered soft steroids and reference steroids on thymus weight in rats.

Test Compound	Amount of Test Compound Applied (μmol)	Number of Rats	mg Thymus / 100 g Rat ± SD	Total Weight per Rat (g) Starting	Final	% Gain ± SD
None (Control)	—	8	364 ± 29	48.44	61.42	27 ± 6
Hydrocortisone	0.75	8	274 ± 45	49.44	61.15	24 ± 7
Chloromethyl 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate	0.75	8	347 ± 31	48.06	62.10	29 ± 5
Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate	0.75	7	309 ± 24	45.57	60.60	33 ± 6

The change in weight in the thymi is a measure of systemic activity and hence of toxicity. The lower the weight of the thymi, the greater the systemic activity. As can be seen from the above data, even hydrocortisone, the natural glucocorticoid, causes a significant decrease in thymus weight compared to the control. The decreases caused by equal doses of representative species of the invention are much less significant, indicating those compounds have much less systemic activity than hydrocortisone.

BLANCHING STUDIES

MeKenzie-type human blanching studies were undertaken to study the blanching effects of a representative test compound of the invention, chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate. The ability of a compound to cause blanching in humans has been found to correlate closely with its anti-inflammatory activity.

The test compound was dissolved in ethanol/isopropyl myristate (90/10 or 70/30) at 0.03, 0.01, 0.003, 0.001 and 0.0003M concentrations. 50 Microliter aliquots of each solution were applied to separate gauze portions of a bandage of the type commonly used for allergy testing and the bandage was applied to the forearm. After 6 hours of occlusion, the bandage was removed. After 1 to 5 hours after removal of the bandage, blanching was observed even at the lowest concentrations of test compound.

When hydrocortisone was tested according to the above procedure comparing it directly to the test compound, blanching was not observed at concentrations of hydrocortisone below 0.03M. Further, it was noted that 0.03M hydrocortisone caused approximately the same degree of blanching as that resulting from use of 0.001M chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

EAR EDEMA TEST

The test animals were Sprague/Dawley rats weighing approximately 150 grams each. In treatment groups, selected amounts of the test compound were dissolved in acetone containing 5% croton oil and 50 microliters of the solution were applied to the inner surface of the right ear of the rats. A control group was identically treated with vehicle only, i.e. 5% croton oil in acetone. Six hours after croton oil challenge, a constant region of each ear was removed by dissection under anesthesia. Then, 48 hours after steroid treatment, the animals were sacrificed and the thymi and adrenals were removed and weighed. The test results showing the inhibitory effect of topically applied steroids on the ear swelling induced by croton oil are summarized in Table II below.

TABLE II

Effect of topically applied soft steroid and reference steroids on ear swelling induced by croton oil.

Test Compound	Dose[a] mg/kg	Number of Test Animals	Ear Weight (mg)[b] Inflamed Ear	Ear Weight (mg)[b] Untreated Ear	% Increase	% Inhibition	Relative Organ Weight (mg/100 g body wt.) Thymus	Relative Organ Weight (mg/100 g body wt.) Adrenals
None (Control)		5	75.2 ± 4.5	46.6 ± 1.4	61.4 ± 8.9		333 ± 15	23.3 ± 1.7
Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate	0.3	5	62.2 ± 3.0*	50.8 ± 2.4	23.3 ± 7.2*	62.1	290 ± 25	26.0 ± 2.5
	1	5	55.0 ± 2.6**	48.4 ± 1.0	14.0 ± 6.5**	77.2	293 ± 21	18.7 ± 1.4
	3	5	52.6 ± 1.8**	51.6 ± 3.2	3.7 ± 8.1**	94.0	288 ± 21	20.3 ± 0.8
Hydrocortisone 17-butyrate	1	5	50.0 ± 2.3**	52.0 ± 2.5	−3.6 ± 3.5**	106.0	303 ± 21	20.2 ± 0.7
Betamethasone 17-valerate	1	5	55.4 ± 1.2*	50.4 ± 2.0	10.9 ± 6.3**	82.2	267 ± 19*	18.9 ± 1.9

[a]calculated values based on application of 50 μl of steroid solution.
[b]50 μl of 5% croton oil/acetone and drugs in 5% croton oil/acetone were applied to the right ear. Ear weight was measured 6 hr after topical application.
*$p < 0.05$; **$p < 0.01$: Significant difference from control.

As can be seen from Table II above, the representative species of the present invention, namely chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, substantially inhibited the swelling (and consequent increased weight) of the ear caused by the croton oil, i.e., the compound exhibited substantial anti-inflammatory activity. On the other hand, in contrast to the effect caused by betametasone 17-valerate, the representative compound of the invention did not significantly decrease the thymus weight as compared to the control, i.e., it did not show a significant degree of systemic activity.

GRANULOMA FORMATION TEST

The test compound was dissolved in acetone and aliquots of varying concentrations were injected into cotton pellets. The pellets were dried and then one pellet was implanted beneath the skin of each test rat. Six days later, the animals were sacrificed and the granulation tissue (granuloma) which formed in and around the implanted pellet was removed, dried and weighed. In addition, the thymi and adrenals were removed and weighed. The ability of a compound to inhibit granuloma formulation in this test is a direct indication of local anti-inflammatory activity; thus, the lower the weight of granulation tissue, the better the anti-inflammatory activity. On the other hand, a significant decrease in thymus weight is indicative of significant systemic activity; conversely, when a test compound does not significantly decrease thymus weight as compared to the control, such is indicative of a lack of (or very minimal) systemic side effects.

The results are tabulated in Tables III, IV and V-a and V-b below.

TABLE III

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Dose (mg/pellet)	Number of Test Animals	Body wt. gain (g)	Granulation tissue Dry wt. (mg/100 g body wt.)	Granulation tissue Inhibition (%)	Relative organ weight mg/100 g body wt. (Decrease %) Thymus	Relative organ weight mg/100 g body wt. (Decrease %) Adrenals
None (Control)		10	40.5 ± 0.8	43.7 ± 4.2		326 ± 22	23.7 ± 1.1
Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate	0.1	8	36.0 ± 2.8	34.7 ± 4.3	20.6	282 ± 13 (13.5)	22.9 ± 2.6 (3.4)
	0.3	8	33.0 ± 1.3***	25.3 ± 2.3**	42.1	298 ± 16 (8.6)	22.8 ± 1.0 (3.8)
	1	8	32.8 ± 0.9***	14.0 ± 1.8***	68.0	304 ± 10 (6.7)	21.8 ± 1.3 (8.0)
	3	7	30.7 ± 1.5***	18.7 ± 2.3***	57.2	278 ± 21 (14.7)	19.6 ± 1.1* (17.3)
Chloromethyl 11β-hydroxy-17α-methoxy-carbonyloxyandrost-4-en-3-one-17β-carboxylate	1	7	33.4 ± 1.3***	24.6 ± 2.6**	43.7	218 ± 15** (33.1)	19.1 ± 1.1** (19.4)
Hydrocortisone 17-butyrate	1	8	33.4 ± 1.4***	32.2 ± 5.0	26.3	73 ± 5*** (77.6)	27.1 ± 1.4 (−14.3)
	3	8	15.9 ± 1.4***	21.6 ± 2.2**	50.6	47 ± 3*** (85.6)	16.5 ± 1.2*** (30.4)
	10	8	4.9 ± 1.0***	29.2 ± 3.1*	33.2	32 ± 3*** (90.2)	16.8 ± 1.2*** (29.1)
Betamethasone 17-valerate	1	8	16.6 ± 1.9***	35.4 ± 7.3	19.0	47 ± 2*** (85.6)	15.5 ± 1.3*** (34.6)
	3	8	14.9 ± 1.7***	31.6 ± 2.1*	27.7	38 ± 3*** (88.3)	13.6 ± 0.9*** (42.6)
	10	8	17.0 ± 2.1***	40.7 ± 2.6	6.9	43 ± 4*** (86.8)	12.6 ± 0.9*** (46.8)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (mean ± S.E.)

TABLE IV

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Dose (μg pellet)	Number of Test Animals	Body wt. gain (g)	Granulation tissue Wet wt. (mg)	Granulation tissue Inhibition (%)
None (Control)		10	32.4 ± 1.4	566 ± 28	
Chloromethyl 11β-hydroxy-	100	8	34.9 ± 2.7	485 ± 36	14.3
17α-isopropoxycarbonyloxy-	300	8	33.9 ± 1.6	431 ± 20**	23.9
androst-4-en-3-one-17β-	1000	8	34.0 ± 2.6	305 ± 16***	46.1
carboxylate	3000	8	32.4 ± 2.3	292 ± 7***	48.4
Chloromethyl 11β-hydroxy-	30	8	32.4 ± 1.2	432 ± 15**	23.7
17α-isopropoxycarbonyloxy-	100	7	35.0 ± 1.5	417 ± 27**	26.3
androsta-1,4-dien-3-one-	300	8	34.4 ± 1.1	369 ± 18***	34.8
17β-carboxylate	1000	8	29.4 ± 1.5	289 ± 12***	48.9
Chloromethyl 17α-ethoxy-	0.3	8	32.4 ± 1.1	472 ± 23*	16.6
carbonyloxy-9α-fluoro-11β-	1	8	37.3 ± 1.5*	388 ± 31***	31.4
hydroxy-16α-methylandrosta-	3	8	34.3 ± 1.1	331 ± 11***	41.5
1,4-dien-3-one-17β-carboxylate	10	8	36.1 ± 1.1	313 ± 13***	44.7
	30	8	31.3 ± 1.4	290 ± 10	48.8
Chloromethyl 9α-fluoro-11β-	1	7	33.0 ± 1.7	423 ± 19**	25.3
hydroxy-17α-isopropoxy-	3	8	30.4 ± 1.1	351 ± 19***	38.0
carbonyloxy-16β-methylandrosta-	10	8	33.0 ± 1.5	362 ± 8***	36.0
1,4-dien-3-one-17β-carboxylate	30	8	31.8 ± 1.7	315 ± 12***	44.3
Hydrocortisone	300	6	26.2 ± 1.7*	333 ± 21***	41.2
17-butyrate	1000	6	26.2 ± 1.2**	366 ± 24***	35.3
	3000	6	6.7 ± 2.2***	329 ± 14***	41.9
	10000	6	−2.0 ± 2.4***	311 ± 7***	45.1
Betamethasone	100	7	24.9 ± 1.9**	400 ± 19***	29.3
17-valerate	300	8	22.3 ± 1.2***	347 ± 15***	38.7
	1000	7	5.3 ± 1.0***	363 ± 28***	35.9
	3000	8	6.6 ± 1.4***	374 ± 15***	33.9

Test Compound	Granulation tissue Dry wt. (mg)	Granulation tissue Inhibition (%)	Thymus wt. mg	Thymus wt. (Decrease %)
None (Control)	81.2 ± 6.3		445 ± 20	
Chloromethyl 11β-hydroxy-	70.0 ± 6.0	13.8	452 ± 29	
17α-isopropoxycarbonyloxy-	50.9 ± 2.8**	37.3	469 ± 25	
androst-4-en-3-one-17β-	24.1 ± 2.7***	70.3	464 ± 30	
carboxylate	20.3 ± 1.3***	75.0	459 ± 24	
Chloromethyl 11β-hydroxy-	51.0 ± 2.8**	37.2	523 ± 26*	
17α-isopropoxycarbonyloxy-	41.1 ± 5.8***	49.4	537 ± 31*	
androsta-1,4-dien-3-one-	38.1 ± 5.9***	53.1	525 ± 28*	
17β-carboxylate	18.5 ± 2.4***	77.2	423 ± 26	
Chloromethyl 17α-ethoxy-	57.3 ± 5.0*	29.4	492 ± 26	
carbonyloxy-9α-fluoro-11β-	36.4 ± 2.4***	55.2	519 ± 22*	
hydroxy-16α-methylandrosta-	27.4 ± 2.9***	66.3	472 ± 16	
1,4-dien-3-one-17β-	22.1 ± 3.6***	72.8	521 ± 35	
carboxylate	20.4 ± 2.4***	74.9	505 ± 26	
Chloromethyl 9α-fluoro-11β-	44.4 ± 5.4***	45.3	526 ± 30*	
hydroxy-17α-isopropoxy-	26.9 ± 4.4***	66.9	471 ± 20	
carbonyloxy-16β-methyl-	29.9 ± 3.3***	63.2	474 ± 25	
androsta-1,4-dien-3-one-	19.9 ± 2.3***	75.5	489 ± 26	
17β-carboxylate				
Hydrocortisone	34.0 ± 5.3***	58.1	353 ± 37*	(20.7)
17-butyrate	35.3 ± 4.2***	56.5	99 ± 7***	(77.8)
	28.0 ± 2.7***	65.5	58 ± 5***	(87.0)
	27.2 ± 2.4***	66.5	46 ± 7***	(89.7)
Betamethasone	41.1 ± 2.7***	49.4	364 ± 24*	(18.2)
17-valerate	33.3 ± 3.6***	59.0	264 ± 29***	(40.7)
	38.1 ± 4.8***	53.1	77 ± 5***	(82.7)
	43.0 ± 4.1***	47.0	63 ± 3***	(85.8)

*p < 0.05, **p < 0.01, ***p < 0.001. (Mean ± S.E.)

TABLE V-a

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Dose (μg/pellet)	Number of Test Animals	Body wt. gain (g)	Granulation Tissue Wet wt. (mg)	Granulation Tissue Inhibition (%)
None (Control)		10	33.5 ± 1.0	525 ± 19	
Chloromethyl 17α-ethoxy-	0.3	8	32.5 ± 1.1	499 ± 36	5.0
carbonyloxy-9α-fluoro-	1	8	36.3 ± 0.9	437 ± 24*	16.8
11β-hydroxy-16β-methyl-	3	8	33.8 ± 1.3	422 ± 32*	19.6
androsta-1,4-dien-3-one-	10	8	31.1 ± 1.7	370 ± 21***	29.5
17β-carboxylate					
Chloromethyl 9α-fluoro-11β-	0.3	8	35.6 ± 1.0	454 ± 27*	13.5

TABLE V-a-continued

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

hydroxy-16α-methyl-17α-	1	8	31.9 ± 0.8	415 ± 30**	21.0
propoxycarbonyloxyandrosta-	3	7	34.1 ± 1.9	360 ± 18***	31.4
1,4-dien-3-one-17β-	10	8	33.1 ± 1.6	350 ± 13***	33.3
carboxylate					
Betamethasone	10	6	31.8 ± 1.6	375 ± 19***	28.6
17-valerate	30	6	30.8 ± 3.0	412 ± 42*	21.5
	100	6	25.7 ± 1.2***	419 ± 20**	20.2
Clobetasol	1	8	33.0 ± 1.2	401 ± 29**	23.6
17-propionate	3	7	24.9 ± 1.8***	402 ± 40**	23.4
	10	8	25.0 ± 2.1**	364 ± 25***	30.7
	30	8	24.8 ± 1.1***	320 ± 10***	39.0
	100	8	15.9 ± 1.0***	325 ± 12***	38.1

Test Compound	Granulation Tissue Dry wt. (mg)	Inhibition (%)	Thymus wt. mg	(Decrease %)
None (Control)	80.1 ± 5.1		495 ± 36	
Chloromethyl 17α-ethoxy-	61.8 ± 5.7*	22.8	501 ± 29	
carbonyloxy-9α-fluoro-	57.0 ± 6.2*	28.8	566 ± 31	
11β-hydroxy-16β-methyl-	47.5 ± 5.0***	40.7	500 ± 27	
androsta-1,4-dien-3-one-	34.8 ± 5.5***	56.6	421 ± 30	
17β-carboxylate				
Chloromethyl 9α-fluoro-11β-	55.1 ± 6.2**	31.2	523 ± 28	
hydroxy-16α-methyl-17α-	42.9 ± 5.1***	46.4	453 ± 21	
propoxycarbonyloxyandrosta-	29.7 ± 3.2***	62.9	504 ± 42	
1,4-dien-3-one-17β-	28.5 ± 2.8***	64.4	547 ± 26	
carboxylate				
Betamethasone	38.5 ± 6.2***	51.9	479 ± 25	(3.2)
17-valerate	46.2 ± 7.4**	42.3	484 ± 23	(2.2)
	41.0 ± 4.2***	48.8	378 ± 30*	(23.6)
Clobetasol	42.0 ± 5.8***	47.6	478 ± 22	(3.4)
17-propionate	43.1 ± 8.9**	46.2	449 ± 21	(9.3)
	37.9 ± 6.8***	52.7	322 ± 22**	(34.9)
	25.5 ± 2.1***	68.2	174 ± 26***	(64.8)
	23.9 ± 3.3***	70.2	84 ± 3***	(83.0)

*p < 0.05, **p < 0.01, ***p < 0.001. (Mean ± S.E.)

TABLE V-b

Effect of locally administered soft steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

Test Compound	Dose (μg/pellet)	Number of Test animals	Body wt. gain (g)	Dry granulation Tissue mg	Inhibition %	Thymus wt. mg
None (Control)	—	10	28.0 ± 1.5	67.2 ± 3.4		505 ± 22
Chloromethyl 9α-fluoro-17α-	1	8	28.9 ± 1.1	59.1 ± 5.8	12.1	441 ± 24
isopropoxycarbonyloxy-16β-	3	8	25.8 ± 0.9	49.4 ± 37**	26.5	519 ± 31
methylandrosta-1,4-dien-	10	7	28.4 ± 0.8	51.1 ± 5.8*	24.0	547 ± 35
3,11-dione-17β-carboxylate	30	8	27.4 ± 0.9	40.6 ± 3.6***	39.6	536 ± 24
Chloromethyl 17α-ethoxy-	1	7	23.7 ± 1.5	55.3 ± 2.6*	17.7	459 ± 41
carbonyloxy-9α-fluoro-16α-	3	8	25.6 ± 1.2	51.6 ± 5.9*	23.2	467 ± 21
methylandrosta-1,4-dien-	10	8	26.5 ± 2.5	41.5 ± 4.7***	38.2	544 ± 31
3,11-dione-17β-carboxylate	30	8	20.3 ± 0.9**	39.9 ± 3.6***	40.6	463 ± 24

*p 0.05, **p 0.01, ***p 0.001. (Mean ± S.E.)
Male Sprague-Dawley rats, weighing 152-189 g (mean body weight 171 g), were used. Cotton pellet weight was 30.1 + 0.3 mg (number of test animals were 30).

The test data in Tables III, IV and V-a and V-b above clearly show that the representative compounds of the present invention exhibited a significant anti-inflammatory response at lower dosages than did the prior art steroids, hydrocortisone 17-butyrate and betamethasone 17-valerate. On the other hand, all of the prior art steroids dramatically decreased the weight of the thymi and thus showed very potent systemic activity, while the representative compounds of the invention either did not significantly decrease the thymi weights or only minimally decreased the thymi weight. Thus, the present compounds have a much greater therapeutic index, i.e., separation of local anti-inflammatory from systemic activity, than do the prior art steroidal anti-inflammatory agents.

Also the test data in Table V-b above shows that the representative compounds of the present invention exhibited a significant local anti-inflammatory activity.

From the results tabulated in Tables IV and V-b, the ED_{40}'s, ED_{50}'s and ED_{60}'s and the relative potencies of representative compounds of the invention were calculated and are shown in Table VI below. One of the compounds of the invention, namely chloromethyl 11-hydroxy-17-isopropoxycarbonyloxyandrost-4-en-3-one-17-carboxylate, has been asigned a potency value of 1 at each ED level, and the potencies of the other compounds are expressed relative thereto. The ED_{40}'s, ED_{50}'s and ED_{60}'s are the dosages required to achieve, respectively, 40%, 50% and 60% reduction in the weight of the granulation tissue.

TABLE VI

Relative potencies of soft steroids in the local cotton pellet granuloma assay.

Test Compound	ED_{40}[1] (μg/pellet)	Relative potency	ED_{50}[2] (μg/pellet)	Relative potency	ED_{60}[3] (μg/pellet)	Relative potency
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-one-17β-carboxylate	307 (238–394)	1	460 (360–623)	1	690 (523–1023)	1
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	47 (15–85)	6.5	119 (60–202)	3.9	301 (178–627)	2.3
Chloromethyl 17α-ethoxy-carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.47 (0.23–0.75)	653	1.07 (0.66–1.59)	430	2.44 (1.65–3.86)	283
Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.25 (0.004–0.886)	1228	0.97 (0.08–2.31)	474	3.75 (1.25–7.68)	184
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	2.31 (1.07–6.38)	133	6.45 (2.96–44.58)	71	18.01 (6.47–393.8)	38
Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	0.58 (0.20–1.01)	529	1.20 (0.67–2.88)	383	2.49 (1.37–13.32)	277
Hydrocortisone 17-butyrate	—	—	—	—	1015 (724–26866)	0.7
Clobetasol 17-propionate	—	—	>3	—	>10	—

[1]dose causing 40% inhibition of granulation tissue weight.
[2]dose causing 50% inhibition of granulation tissue weight.
[3]dose causing 60% inhibition of granulation tissue weight.
( ) = 95% confidence limits

THYMUS INHIBITION TESTING

Several further studies were undertaken to determine the effects of selected compounds of the invention on thymi weights in rats when the drugs were systemically administered. In each of these studies, male Sprague-Dawley rats were used. (For average weight of rats for each study, see the tables which follow.) The test compounds were suspended in 0.5% CMC (carboxymethylcellulose) and injected subcutaneously once daily for three days. On the fifth day (48 hours following the last treatment), the animals were sacrificed and the thymi weights were recorded. Body weight gains were measured 24 hours after the last treatment. The test results are set forth in Tables VII, VIII and IX below. The TED_{40}'s, TED_{50}'s (thymolytic effective doses or doses required to achieve 40% and 50% inhibition of thymi weight, respectively) and relative potency of representative compounds of the invention and reference steroids are shown in Table X below. In Table X, the TED_{40} and TED_{50} for the reference steroid betamethasone 17-valerate has each been assigned a value of 1, and the potencies of the other compounds are expressed relative thereto. It is evident that the higher the inhibition of thymus activity at a given dose, the more toxic the compound is.

TABLE VII

Effects of systemically administereed (s.c.) soft steroids and reference steroids on body weight and thymus weight in rats.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body weight gain (g)	Thymus (mg)	Inhibition (%)
None (Control)		9	18.3 ± 0.7	471 ± 21	
Chloromethyl 11β-hydroxy-	3	9	14.7 ± 0.6**	439 ± 18	6.8
17α-isopropoxycarbonyloxy-	10	10	10.2 ± 0.7***	386 ± 17**	18.0
androst-4-en-3-one-17β-	30	10	6.8 ± 2.1***	291 ± 22***	38.2
carboxylate	100	10	2.8 ± 1.8***	185 ± 17***	60.7
Chloromethyl 11β-hydroxy-	3	9	9.0 ± 0.9***	377 ± 16**	20.0
17α-isopropoxycarbonyl-	10	9	6.2 ± 0.7***	312 ± 23***	33.8
oxyandrosta-1,4-dien-3-	30	10	4.8 ± 1.4***	257 ± 24***	45.4
one-17β-carboxylate	100	10	0.3 ± 1.6***	161 ± 19***	65.8
Chloromethyl 17α-ethoxy-	1	10	13.1 ± 1.0***	428 ± 20	9.1
carbonyloxy-9α-fluoro-	3	9	12.7 ± 1.4**	412 ± 20	12.5
11β-hydroxy-16α-methyl-	10	10	9.7 ± 1.3***	405 ± 21*	14.0
androsta-1,4-dien-3-one-	30	10	4.4 ± 0.7***	292 ± 15***	38.0
17β-carboxylate					
Hydrocortisone	0.3	10	17.0 ± 0.8	441 ± 27	6.4
17-butyrate	1	10	11.8 ± 0.8***	323 ± 16***	31.4
	3	10	7.3 ± 0.5***	166 ± 5***	64.8
	10	10	−5.0 ± 1.1***	65 ± 5***	86.2
Betamethasone	0.1	10	15.5 ± 0.9*	362 ± 16***	23.1
17-valerate	0.3	10	12.4 ± 0.9***	276 ± 11***	41.4
	1	10	13.0 ± 1.1***	200 ± 14***	57.5

TABLE VII-continued

Effects of systemically administereed (s.c.) soft steroids and reference steroids on body weight and thymus weight in rats.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body weight gain (g)	Thymus (mg)	Inhibition (%)
	3	10	9.9 ± 1.3***	119 ± 7***	74.7

*p < 0.05, **p < 0.01, ***p < 0.001 (Mean ± S.E.)
Male Sprague-Dawley rats, weighing 149–168 g, were used.

TABLE VIII

Effects of systemically administered (s.c.) soft steroids and reference steroids on body weight and thymus weight in rats.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body weight gain (g)	Thymus wt. (mg)	Inhibition (%)
None (Control)		10	18.9 ± 0.6	550 ± 24	
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methyl-androsta-1,4-dien-3-one-17β-carboxylate	10	7	14.2 ± 1.9	533 ± 31	3.1
Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	10	7	2.7 ± 1.9***	234 ± 31***	57.5
Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	10	7	5.3 ± 1.4***	260 ± 26***	52.7
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	10	7	2.4 ± 1.8***	266 ± 20***	51.6
Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate	10	7	2.7 ± 1.7***	277 ± 25***	49.6
Clobetasol	0.003	8	18.2 ± 0.6	537 ± 28	2.4
17-propionate	0.01	8	15.5 ± 1.1*	498 ± 15	9.5
	0.03	8	12.3 ± 1.3**	363 ± 22***	34.0
	0.1	8	−0.4 ± 1.3***	149 ± 9***	72.9
	0.3	8	−14.3 ± 1.3***	63 ± 3***	88.5

*p < 0.05, **p < 0.01, ***p < 0.001. (mean ± S.E.)
Male Sprague-Dawley rats, weighing about 185 g (162–209 g), were used.

TABLE IX

Effects of systemically administered (s.c.) soft steroids on body weight and thymus weight in rats.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body weight gain (g)	Thymus wt. (mg)	Decrease (%)
None (Control)		10	21.2 ± 0.9	426 ± 17	
Chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	3	7	18.8 ± 1.4	426 ± 19	0.0
	10	7	13.8 ± 1.6***	354 ± 8**	16.9
	30	7	12.0 ± 0.8***	282 ± 11***	33.8
	100	7	9.8 ± 1.3***	206 ± 15***	51.6
Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	1	7	18.0 ± 1.5	387 ± 23	9.2
	3	7	15.6 ± 1.3**	347 ± 15**	18.5
	10	7	17.4 ± 1.5*	357 ± 22*	16.2
	30	7	13.5 ± 1.0***	335 ± 17**	21.4

*p < 0.05, **p < 0.01, ***p < 0.001 (Mean ± S.E.)
Male Sprague-Dawley rats, weighing 91–112 g, were used.

TABLE X

Thymolytic activities of soft steroids administered subcutaneously to rats.

Compound	TED_{40} (mg)	Relative Potency	TED_{50} (mg)	Relative Potency
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate	31.0 (23.9–41.9)	0.01	58.5 (43.1–87.1)	0.01
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	16.2 (11.2–23.2)	0.02	35.3 (24.6–57.5)	0.02
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	51.5 (26.5–290.0)	0.0058	>51.5[a]	<0.011
Hydrocortisone 17-butyrate	1.3 (1.1–1.5)	0.23	2.0 (1.7–2.3)	0.29
Betamethasone	0.30	1	0.58	1

TABLE X-continued

Thymolytic activities of soft steroids administered subcutaneously to rats.

Compound	TED_{40} (mg)	Relative Potency	TED_{50} (mg)	Relative Potency
17-valerate	(0.24–0.36)		(0.49–0.69)	
Clobetasol	0.035	8.6	0.052	11.2
17-propionate	(0.030–0.039)		(0.046–0.059)	

[a]Even at a dosage level of 100 mg/kg/day, 50% reduction in thymus weight could not be achieved.

BLANK COTTON PELLET GRANULOMA ASSAY

A further test was undertaken to determine the thymolytic activity of a representative species of the invention as compared to betamethasone 17-valerate. In this test, the drugs were administered intravenously to rats, while using a blank cotton pellet granuloma assay. Male Sprague-Dawley rats, each weighing about 185 grams (166–196 grams), were used. Two cotton pellets, each weighing 30 mg and containing no test compounds, were sterilized and implanted subcutaneously into the back of each test animal. This day was considered day 0 of implantation. Test compounds suspended in 0.8% polysorbate 80 were administered intravenously once daily for 3 consecutive days beginning with day 1. On day 5, the animals were sacrificed and the two pellets, with their respective granulomas, were removed, dried overnight in an oven at 50° C. and weighed (dry granuloma weight). The thymi and final body weights were also recorded. The results are given in Table XI below.

In the foregoing tests, there was determined the deactivation of the representative species of the present soft steroids administered intravenously to rats. The ratio between the potencies of the test steroids and betamethasone 17-valerate against local anti-inflammation was 283:0.7 as seen from Table VI. This means that the test compounds exhibit a local anti-inflammatory activity which is approximately 400 times as high as the activity of the betamethasone 17-valerate. The test compounds were administered intravenously to rats to check the test compounds also for systemic anti-inflammatory activity as compared to betamethasone 17-valerate. The test compounds were found lower in the inhibition of granulation tissue formation and also in the thymus involution activity than betamethasone 17-valerate. From the results of the tests, it is presumed that the compounds which will not be readily subjected to metabolism (deactivation) have a systemic anti-inflammatory activity, as is the case with betamethasone 17-valerate.

TABLE XI

Thymolytic activities of test steroids administered intravenously to rats in the blank cotton pellet granuloma assay.

Test Compound	Dose (mg/kg/day)	Number of Test Animals	Body wt. gain (g)	Dry granuloma wt. (mg)	Inhibition (%)	Thymus wt. (mg)	Decrease (%)
None (Control)		7	21.4 ± 1.3	62.7 ± 6.1		422 ± 27	
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	1	7	14.1 ± 1.4**	50.1 ± 6.9	20.1	373 ± 25	11.6
	3	6	14.2 ± 1.3**	49.3 ± 5.1	21.4	338 ± 20*	19.9
	10	6	0.3 ± 1.7***	45.7 ± 4.6	27.1	209 ± 31***	50.5
	30	6	−18.5 ± 2.3***	32.7 ± 3.0**	47.8	71 ± 4***	83.2
Betamethasone 17-valerate	0.1	7	14.4 ± 1.6**	49.3 ± 3.9	21.4	305 ± 14**	27.7
	0.3	5	12.2 ± 1.1***	44.4 ± 2.8*	29.2	288 ± 27**	31.8
	1	7	12.9 ± 1.1***	46.1 ± 4.3*	26.5	233 ± 15***	44.8
	3	7	13.0 ± 2.5*	47.3 ± 2.7	24.6	167 ± 22***	60.4

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$. (Mean ± S.E.)

The ED_{50}'s calculated for the local cotton pellet granuloma assay (as shown, for example, in Table VI above) and the TED_{40}'s calculated on the basis of thymus inhibition testing (as shown, for example, in Table X above) were used to arrive at relative potency and a therapeutic index for representative species of the invention as compared to prior art steroids. See Table XII below, which clearly shows the potent anti-inflammatory activity and minimal systemic toxicity of the compounds of the present invention.

TABLE XII

Therapeutic Indices of representative species of the invention as compared to prior art steroids.

Compound	ED_{50}[a]	Relative Potency	TED_{40}[b]	Relative Potency	Therapeutic Index[c]
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate	460 (360–623)	1	31.0 (23.9–41.9)	1/24	24
Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate	119 (60–202)	4	16.2 (11.2–23.2)	1/12	48
Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	1.07 (0.66–1.59)	450	51.5 (26.5–290.0)	1/40	18000
Chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	2.38 (1.60–3.78)	202	46.0 (36.0–62.1)	1/36	7270
Hydrocortisone	480	1	1.3	1	1

TABLE XII-continued

Therapeutic Indices of representative species of the invention as compared to prior art steroids.

Compound	ED_{50}[a]	Relative Potency	TED_{40}[b]	Relative Potency	Therapeutic Index[c]
17-butyrate	(313–892)		(1.1–1.5)		
Betamethasone	100	5	0.3	4	1
17-valerate			(0.24–0.36)		

[a]for the anti-inflammatory effect in cotton pellet granuloma (μg/pellet)
[b]for the thymus inhibition effect required subcutaneously (mg/kg)
[c]the ratio of the relative potency for the ED_{50} to the relative potency for the TED_{40}; hydrocortisone 17-butyrate has been assigned a value of one

The compounds of formula (I) can be combined with suitable non-toxic pharmaceutically acceptable carriers to provide pharmaceutical compositions for use in the treatment of topical or other localized inflammation. Obviously, in view of their lack of systemic activity, the compounds of the present invention are not intended for treatment of conditions where systemic adrenocortical thereapy is indicated, e.g., adrenocortical insufficiency. As examples of inflammatory conditions which can be treated with pharmaceutical compositions containing at least one compound of the invention and one or more pharmaceutical carriers, the following can be mentioned. dermatological disorders such as atopic dermatitis, acne, psoriasis or contact dermatitis; allergic states such as bronchial asthma; ophthalmic and otic diseases involving acute and chronic allergic and inflammatory reactions; respiratory diseases; ulcerative colitis; and anorectal inflammation, pruritus and pain associated with hemorrhoids, proctitis, cryptitis, fissures, postoperative pain and pruritus ani. Such compositions may also be applied locally as a propylactic measure against the inflammation and tissue rejection which arise in connection with transplants.

Obviously, the choice of carrier(s) and dosage forms will vary with the particular condition for which the composition is to be administered.

Examples of various types of preparations for topical/local administration include ointments, lotions, creams, powders, drops, (e.g. eye or ear drops), sprays, (e.g. for the nose or throat), suppositories, retention enemas, chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) and aerosols. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or glycols. Such base may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a glycolic solvent such as propylene glycol or 1,3-butanediol. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, polyethylene glycols, woolfat, hydrogenated lanolin and beeswax and/or glyceryl monostearate and/or nonionic emulsifying agents.

The solubility of the steroid in the ointment or cream may be enhanced by incorporation of an aromatic alcohol such as benzyl alcohol, phenylethyl alcohol or phenoxyethyl alcohol.

Lotions may be formulated with an aqueous or oily base and will in general also include one or more of the following, namely, emulsifying agents, dispersing agents, suspending agents, thickening agents, solvents, coloring agents and perfumes. Powders may be formed with the aid of any suitable powder base e.g. talc, lactose or starch. Drops may be formulated with an aqueous base also comprising one or more dispersing agents, suspending agents or solubilizing agents, etc. Spray compositions may, for example, be formulated as aerosols with the use of a suitable propellane, e.g., dichlorodifluoromethane or trichlorofluoromethane.

The proportion of active ingredient in the compositions according to the invention will vary with the precise compound used, the type of formulation prepared and the particular condition for which the composition is to be administered. The formulation will generally contain from about 0.0001 to about 5% by weight of the compound of formula (I). Topical preparations will generally contain 0.0001 to 2.5%, preferably 0.01 to 0.5%, and will be administered once daily, or as needed. Also, generally speaking, the compounds of the invention can be incorporated into topical and other local compositions formulated substantially as are such presently available types of compositions containing known glucocorticosteroids, at approximately the same (or in the case of the most potent compounds of the invention, at proportionately lower) dosage levels as compared to known highly active agents such as methyl prednisolone acetate and beclomethasone dipropionate or at considerably lower dosage levels as compared to less active known agents such as hydrocortisone.

Thus, for example, an inhalation formulation suitable for use in the treatment of asthma can be prepared as a metered-dose aerosol unit containing a representative species of the invention such as chloromethyl 17α/ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, according to procedures well-known to those skilled in the art of pharmaceutical formulations. Such an aerosol unit may contain a microcrystalline suspension of the aforementioned compound in suitable propellants (e.g., trichlorofluoromethane and dichlorodifluoromethane), with oleic acid or other suitable dispersing agent. Each unit typically contains 10 milligrams of the aforesaid active ingredient, approximately 50 micrograms of which are released at each actuation. When one of the more potent species of the invention, e.g. chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate, is employed, each unit typically contains 1 milligram of the active ingredient and releases approximately 5 micrograms at each actuation.

Another example of a pharmaceutical composition according to the invention is a foam suitable for treatment of a wide variety of inflammatory anorectal disorders, to be applied anally or perianally, comprising 0.1% of a compound of formula (I) such as chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrosta-4-en-3-one-17β-carboxylate, and 1% of a local anaesthetic such as pramoxine hydrochloride, in a mucoadhesive foam base of propylene glycol, ethoxylated stearyl alcohol, polyoxyethylene-10-stearyl ether, cetyl alcohol, methyl paraben, propyl paraben, triethanolamine, and water, with inert propellents. When a more potent compound of the invention is employed, less active

ingredient generally is used, e.g. 0.05% of chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

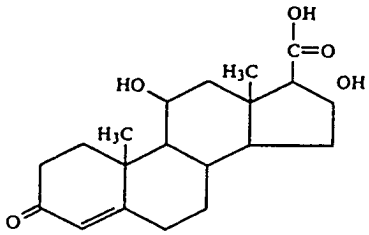
Yet another pharmaceutical formulation according to the invention is a solution or suspension suitable for use as a retention enema, a single dose of which typically contains 40 milligrams of a compound of the invention such as chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate (or 20 milligrams of a more potent compound of the invention such as chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate or chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate) together with sodium chloride, polysorbate 80 and from 1 to 6 ounces of water (the water being added shortly before use). The suspension can be administered as a retention enema or by continuous drip several times weekly in the treatment of ulcerative colitis.

Other pharmaceutical formulations according to the invention are illustrated in the examples which follow.

Without further elaboration, it is believed that one of ordinary skill in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the following examples are to be construed as merely illustrative and not limitative of the remainder of the specification and claims in any way whatsoever.

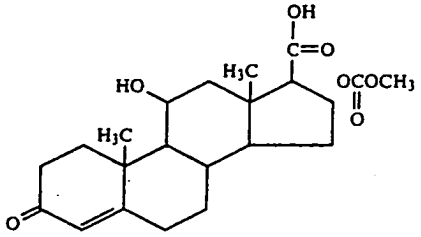
EXAMPLE 1

To a solution of hydrocortisone (15 grams, 0.04 mol) in 120 milliliters of tetrahydrofuran and 30 milliliters of methanol at room temperature is added a warm (approximately 50° C.) solution of sodium metaperiodate (25.7 grams, 0.12 mol) in 100 milliliters of water). The reaction mixture is stirred at room temperature for 2 hours, then is concentrated under reduced pressure to remove the tetrahydrofuran and methanol. The solid is triturated with 50 milliliters of water, separated by filtration, washed with water and dried in vacuo at 50° C. for 3 hours. The product, 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid (i.e., cortienic acid), melts at 231°–234° C., is obtained in approximately 96% yield (13.76 grams), and can be represented by the structural formula



EXAMPLE 2

To a cold solution of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid (5% weight/volume; 1 mol) and triethylamine (4 mol) in dichloromethane is added a 50% (weight/volume) solution of methyl chloroformate (3.9 mol) in dichloromethane. The reaction mixture is allowed to warm to room temperature over a 2 hour period. The triethylamine hydrochloride precipitate which forms is removed by filtration and the filtration is washed successively with 3% sodium bicarbonate, dilute (~1%) hydrochloric acid and water. The organic layer is separated, dried with magnesium sulfate, and filtered. The filtrate is concentrated in vacuo to a foam. The foam is used in the next step (e.g., Example 3 below) or chromatographed and crystallized for analysis. The product, 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid, melts at 198°–204° C. after chromatography and crystallization; ir (KBr) 3000–2800 (C—H), 1750, 1735, 1720 (C=O), 1650, 1640 (C=C—C=O) cm^{-1}. The product can be represented by the structural formula



Substitution of an equivalent quantity of ethyl chloroformate for the methyl chloroformate employed above and substantial repetition of the foregoing procedure affords 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, melting at 192°–195° C. after chromatography and crystalization; ir (KBr) 3500 (11β-O—H), 3000–2800 (C—H), 1740 (C=O), 1630 (C=C—C=O) cm^{-1}, nmr($CDCl_3$) δ6.4(1, b, COOH), 5.67(1, s, C—CH), 4.43 (1, b, CHOE), 4.13 (2, q, J=7.5 Hz, OCH_2CH_3); Anal. calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.76; H, 7.74.

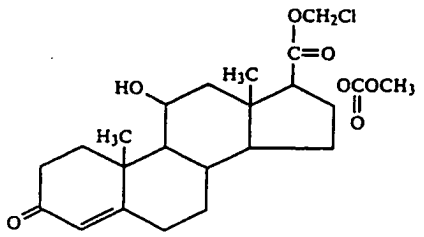
In a similar manner, substitution of an equivalent quantity of butyl chloroformate for the methyl chloroformate employed in the frist paragraph of this example and substantial repetition of the procedure there detailed affords 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid. The final product, after crystallization from tetrahydrofuran-hexane, melts at 164°–166° C.

Similarly, substituting an equivalent amount of isopropyl chloroformate for the methyl chloroformate used in the first paragraph of this example and repeating the procedure there detailed affords 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid. The final product, after crystallization from tetrahydrofuran-hexane, melts at 144.5°–146.5° C.

EXAMPLE 3

11β-Hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid is combined with an equivalent amount of 1N sodium hydroxide in methanol and that solution is diluted to 100 times the original volume with ethyl ether. The suspension which results is refrigerated for 1 hour. Then, the crystals which form are removed by filtration, dried in an evacuated desiccator, and dissolved in hexamethylphosphoramide (10% weight/volume). A portion of the resultant solution containing 1 mole of the acid salt, i.e. of sodium 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, is combined with 4 moles of chloromethyl iodide. The reaction mixture is maintained at room temperature for 3 hours, then is diluted to 10 times the original volume with ethyl acetate. The diluted reaction mixture is washed successively with 5% sodium thiosulfate, 3% sodium bicarbonate, and water.

The organic layer is separated, dried with magnesium sulfate and filtered. The filtrate is concentrated in vacuo to a foam. The foam is purified by crystallization from a suitable solvent (ethyl ether or tetrahydrofuran/hexane). There is thus obtained chloromethyl 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, melting at 171°-173° C. after crystallization; ir(KBr) 3000-2800 (C—H), 1760, 1748 (C=O), 1650 (C=C—C=O) cm^{-1}; nmr ($CDCl_3$) δ5.67(s, 1, C=CH), 5.82, 5.62 (ABq, J=5.5 Hz, 2, OCH_2Cl), 4.47(b, 1, CHOH); Anal. calcd. for $C_{23}H_{31}ClO$: C, 60.72; H, 6.87; Cl, 7.79. Found: C, 60.50; H, 7.06; Cl, 7.50. The product is characterized by the structural formula



Substitution of an equivalent quantity of 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid for the steroidal acid employed above and substantial repetition of the foregoing procedure affords, as the intermediate salt, sodium 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 197°-200° C. after crystallization; ir (KBr) 3600-3200 (O—H), 3000-2800 (C—H), 1763, 1740 (C=O), 1650 (C=C—C=O) cm^{-1}; nmr ($CDCl_3$) δ5.7(s, 1, C=CH), 5.81, 5.62 (ABq, J=5 Hz, 2, —OCH_2Cl); Anal calcd. for $C_{24}H_{33}ClO_7$: C, 61.46; H, 7.09. Found: C, 61.58; H, 7.08.

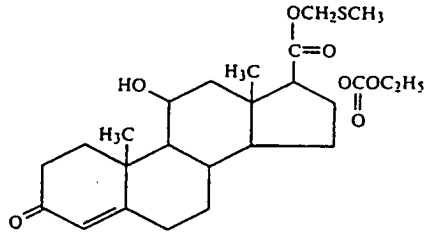
In a similar manner, substitution of an equivalent quantity of 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid for the steroidal acid employed in the first paragraph of this example and substantial repetition of the procedure there detailed affords, as the intermediate salt, sodium 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, chloromethyl 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 98°-100° C. after crystallization; ir(KBr) 3600-3300 (O—H), 3000-2800 (C—H), 1765 (O_2C=O), 1735 (OC=O), 1650 (C=C—C=O) cm^{-1}; nmr($CDCl_3$) δ5.60 (2, ABq, J=4.5 Hz, —OCH_2Cl), 5.67 (1, s, C=CH), 4.45 (1, b, CHOH), 4.08 (2, t, J=6 Hz, O_2COCH_2—CH_2); Anal calcd. for $C_{26}H_{37}ClO_7$: C, 62.77; H, 7.44; Cl, 7.14. Found: C, 62.88; H, 7.23; Cl, 7.30.

Similarly, substituting an equivalent amount of 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid for the steroidal acid employed in the first paragraph of this example and substantial repetition of the procedure there detailed affords, as the intermediate salt, sodium 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, melting at 183.5°-184.5° C. after recrystallization from tetrahydrofuran-hexane.

In a similar manner, an equivalent quantity of 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid is substituted for the steroidal acid and an equivalent quantity of butyl chloride is substituted for the chloromethyl iodide employed in the first paragraph of this example; and the procedure there detailed is substantially repeated, except that the step of washing with 5% sodium thiosulfate is eliminated. Obtained in this manner are the intermediate salt, sodium 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, and the final product, butyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate. The final product after crystallization from acetone melts at 148°-149° C.; after chromatography and crystallization, ir(KBr) 3600-3200 (O—H), 3000-2800 (C—H), 1750 (2 C=O), 1670 (C=C—C=O) cm^{-1}; nmr ($CDCl_3$) δ5.64(s, 1, —C=CH), 4.46 (b, 1, CHOH), 4.32-4.95 (m, 4, $COOCH_2CH_3$+, $COOCH_2CH_2$—); Anal. calcd. for $C_{27}H_{40}O_7$: C, 67.99; H, 8.39. Found: C, 67.76; H, 7.74.

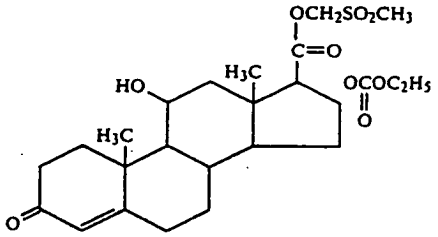
EXAMPLE 4

17α-Ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid (3 grams, 7.13 mmol6) is treated with 7.13 milliliters of 1M methanolic sodium hydroxide solution, and 500 milliliters of ethyl ether are then added to effect precipitation. The precipitate is separated by filtration and dried in an evacuated dessicator overnight to afford 2.71 grams (6.12 mmol) of the desired salt, i.e. sodium 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, as a yellow powder. The salt is dissolved in 40 milliliters of hexamethylphosphoramide and chloromethyl methyl sulfide (2.36 grams, 24.5 mmol) is added slowly. A precipitate of sodium chloride forms in the reaction mixture within 1 minute. The reaction mixture is stirred at room temperature for 1 hour, then is diluted with ethyl acetate to a total volume of 200 milliliters and washed successively with 3% sodium bicarbonate and water. The organic layer is separated, dried with magnesium sulfate and filtered. The filtrate is concentrated in vacuo to an oil, and the oil is chromatographed from silica gel, using ethyl acetate, chloroform and acetic acid as eluants. The chromatographed product is crystallized from a mixture of ethyl ether and hexane to give white powdery crystals of methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 133°-136° C. That product is characterized by the structural formula



To a solution of methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate (0.48 gram, 1 mmol) in 2 milliliters of dichloromethane is added m-chloroperoxybenzoic acid (0.4 gram=0.34 gram of peracid, 2 mmol). An exothermic reaction ensues, which subsides quickly. The reaction mixture is stirred at room temperature for 1 hour. The

precipitate which forms is removed by filtration and the filtrate is concentrated in vacuo to afford, as a white foam, methylsulfonylmethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate. That product has the structural formula



NMR ($CDCl_3$): δ5.07 (s, 2, OCH_2SO_2), 2.97 (s, 3, SO_2CH_3).

Repetition of the procedure described in the preceding paragraph, but using only 1 mmol of m-chloroperoxybenzoic acid, affords methylsulfinylmethyl 17β-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

EXAMPLE 5A

Substitution of an equivalent quantity of one of the starting materials listed below for the hydrocortisone used in Example 1 and substantial repetition of the procedure there detailed affords the indicated products:

STARTING MATERIAL	PRODUCT
fludrocortisone	9α-fluoro-11β,17α-dihydroxy-androst-4-en-3-one-17β-carboxylic acid, m.p. 250–253° C.
betamethasone	9α-fluoro-11β,17α-dihydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid, m.p. 248–249° C.
dexamethasone	9α-fluoro-11β,17α-dihydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid, m.p. 275–278.5° C.

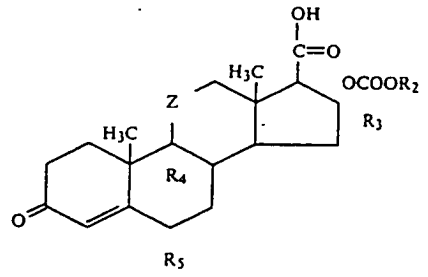
EXAMPLE 5B

Substitution of an equivalent quantity of one of the starting materials listed below for the hydrocortisone used in Example 1 and substantial repetition of the procedure there detailed affords the indicated products:

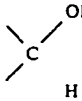
STARTING MATERIAL	PRODUCT
cortisone	17α-hydroxyandrost-4-en-3,11-dione-17β-carboxylic acid
chloroprednisone	6α-chloro-17α-hydroxyandrosta-1,4-dien-3,11-dione-17β-carboxylic acid
flumethasone	6α,9α-difluoro-11β, 17α-dihydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid
fluprednisolone	6α-fluoro-11β,17α-dihydroxy-androsta-1,4-dien-3-one-17β-carboxylic acid
meprednisone	17α-hydroxy-16β-methylandrosta-1,4-dien-3,11-dione-17β-carboxylic acid
methyl prednisolone	11α,17β-dihydroxy-6α-methyl-androsta-1,4-dien-3-one-17β-carboxylic acid
paramethasone	6α-fluoro-11β,17α-dihydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid
prednisolone	11β,17α-dihydroxyandrosta-1,4-dien-3-one-17β-carboxylic acid
prednisone	17α-hydroxyandrosta-1,4-dien-3,11-dione-17β-carboxylic acid
triamcinolone	9α-fluoro-11β,16α,17α-trihydroxy-androsta-1,4-dien-3-one-17β-carboxylic acid

EXAMPLE 6A

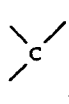
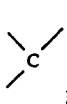
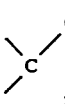
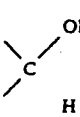
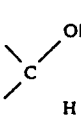
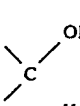
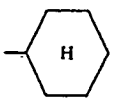
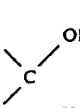
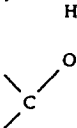
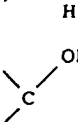
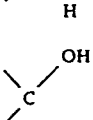
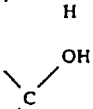
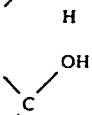
Following the general procedure of Example 2 and substituting therein the appropriate reactants affords the following novel intermediates of the present invention:



Compounds

Compound No.	R_2	R_3	R_4	R_5	Z	Δ	m.p.
6A-1	$CH_2C_6H_5$	H	H	H		4	183–184° C. (ethanol)
6A-2	C_2H_5	H	F	H		4	190–191° C. (THF/hexane)
6A-3	C_2H_5	β-CH_3	F	H		1,4	128–129° C. (THF/hexane)

-continued

Compound No.	R_2	R_3	R_4	R_5	Z	Δ	m.p.
6A-4	C_2H_5	α-CH_3	F	H		1,4	143–144.5° C. (THF/hexane)
6A-5	iso-C_3H_7	α-CH_3	F	H		1,4	154.5–156° C. (THF/hexane)
6A-6	iso-C_4H_9	H	H	H		4	125–126° C. (THF/hexane)
6A-7	iso-C_3H_7	β-CH_3	F	H		1,4	171.5–172.5° C. (THF/hexane)
6A-8	n-C_3H_7	H	H	H		4	156–157° C. (THF/hexane)
6A-9	n-C_3H_7	α-CH_3	F	H		1,4	157–158° C. (THF/hexane)
6A-10		H	H	H		4	156–157.5° C. (ether/hexane)
6A-11	CH_3	α-CH_3	F	H		1,4	180–182° C. (ethyl acetate)
6A-12	n-C_5H_{11}	α-CH_3	F	H		1,4	138.5–139.5° C. (THF/hexane)
6A-13	C_2H_5	α-CH_3	F	F		1,4	157–158° C. (decomp.) (THF/hexane)
6A-14	C_6H_5	α-CH_3	F	H		1,4	246–248° C. (THF/hexane)
6A-15	CH_2CH_2Cl	α-CH_3	F	H		4	93–94° C. (THF/hexane)

6A-1 to 6A-15 above can be named as follows:

6A-1: 17α-benzyloxoycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid

6A-2: 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid

6A-3: 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-4: 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-5: 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-6: 11β-hydroxy-17α-isobutoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid

6A-7: 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-8: 11β-hydroxy-17α-propoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid

6A-9: 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-10: 17α-cyclohexyloxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid

6A-11: 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic aicd

6A-12: 9α-fluoro-11β-hydroxy-16α-methyl-17α-n-pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

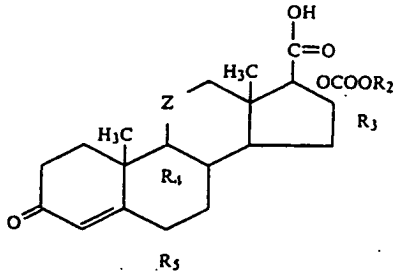
6A-13: 17α-ethoxycarbonyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyllandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-14: 9α-fluoro-11β-hydroxy-16α-methyl-17α-phenoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6A-15: 17α-(2-chloroethoxycarbonyloxy)-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

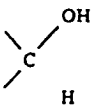
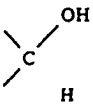
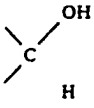
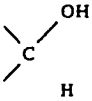
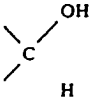
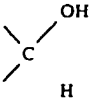
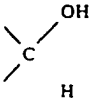
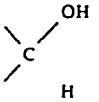
EXAMPLE 6B

Following the general procedure of Example 2 and substituting therein the appropriate reactants affords the following novel intermediates of the present invention:

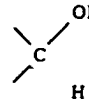
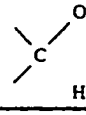


Compound No.	R_2	R_3	R_4	R_5	Z	Δ
6B-1	C_2H_5	H	H	H	C=O	4
6B-2	CH_3	H	H	H	C=O	4
6B-3	CH_3	H	F	H	C(OH)H	4
6B-4	C_2H_5	α-CH_3	F	F	C(OH)H	1,4
6B-5	C_2H_5	H	H	F	C(OH)H	1,4
6B-6	C_2H_5	β-CH_3	H	H	C=O	1,4
6B-7	CH_2CCl_3	H	H	H	C(OH)H	4
6B-8	C_2H_5	α-CH_3	H	F	C(OH)H	1,4
6B-9	C_2H_5	H	H	H	C(OH)H	1,4

-continued

Compound No.	R_2	R_3	R_4	R_5	Z	Δ
6B-10	C_2H_5	H	H	H		1,4
6B-11	C_2H_5	α-$OCOOC_2H_5$	F	H		1,4
6B-12	CH_2Cl	α-CH_3	F	H		1,4
6B-13	CH_2CH_2Cl	α-CH_3	F	H		1,4
6B-14	C_2H_5	H	H	Cl		1,4
6B-15	C_6H_5	H	H	H		4
6B-16		H	H	H		4
6B-17		H	H	H		4
6B-18	$CH=CH_2$	H	H	H		4
6B-19	CH_2OCH_3	H	H	H		4
6B-20	CH_2SCH_3	H	H	H		4
6B-21	$CH_2CH_2NHCOCH_3$	H	H	H		4
6B-22	$CH_2CH_2OCOCH_3$	H	H	H		4
6B-23	C_2H_5	H	H	CH_3		1,4

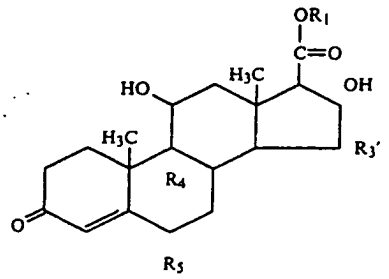
-continued

Compound No.	R_2	R_3	R_4	R_5	Z	Δ
6B-24	$CH_2SO_2CH_3$*	H	H	H		4
6B-25	CH_2SOCH_3*	H	H	H		4

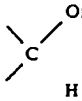
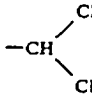
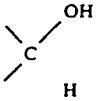
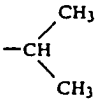
*prepared from 6B-20 by subsequent reaction with m-chloroperbenzoic acid.

EXAMPLE 6C

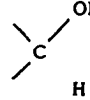
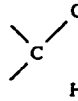
Following the general procedure of Example 2 and substituting therein the appropriate reactants affords the following novel intermediates of the present invention:



(VI)

Compound No.	R_2	R_3	R_4	R_5	Z	Δ	m.p.
6C-1	$-CH_2CH=CH_2$	α-CH_3	F	H		1,4	227–229° C. (THF/hexane)
6C-2	$-CH_2CH_2CH_3$	α-CH_3	F	F		1,4	148–155° C. (decomp.) (ethanol/water)
6C-3		α-CH_3	F	F		1,4	157–159° C. (ethanol/water)
6C-4	$-C_2H_5$	α-CH_3	H	F		1,4	105–108° C. (THF/n-hexane)
6C-5	$-(CH_2)_2CH_3$	α-CH_3	H	F		1,4	150–152° C. (THF/n-hexane)
6C-6		α-CH_3	H	F		1,4	124–127° C. (THF/n-hexane)
6C-7	$-CH_3$	H	H	H		1,4	178–180° C. (THF/n-hexane)
6C-8	$-CH_3$	α-CH_3	H	F		1,4	182–183° C. (THF/n-hexane)

-continued

Compound No.	R_2	R_3	R_4	R_5	Z	Δ	m.p.
6C-9	$-C_2H_5$	H	H	H		1,4	153–156° C. (THF/n-hexane)
6C-10	$-CH_3$	β-CH_3	F	H		1,4	186–188 (decomposition) (THF/n-hexane)
6C-11	$-CH_2CH_2CH_3$	β-CH_3	F	H		1,4	143–144.5° C. (THF/n-hexane)

The foregoing compounds can be named as follows:

6C-1: 17α-allyloxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-2: 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-3: 6α,9α-difluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-4: 17α-ethoxycarbonyloxy-6α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-5: 6α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-6: 6α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-7: 11β-hydroxy-17α-methoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-8: 6α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

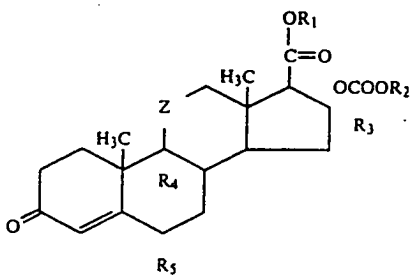
6C-9: 17α-ethoxycarbonyloxy-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylic acid

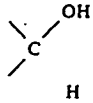
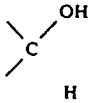
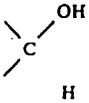
6C-10: 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid

6C-11: 9α-fluoro-11β-hydroxy-16β-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid

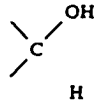
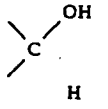
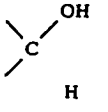
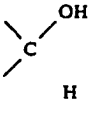
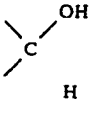
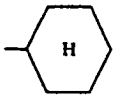
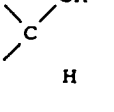
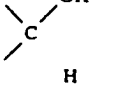
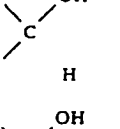
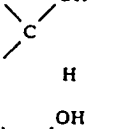
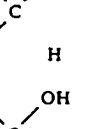
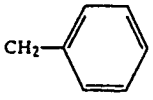
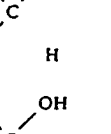
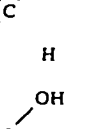
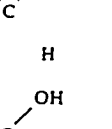
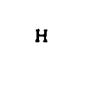
EXAMPLE 7A

Following the general procedure of Example 3 and substituting therein the appropriate reactants affords the following compounds:

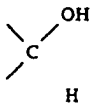
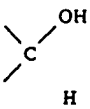
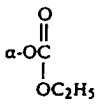
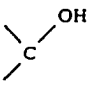
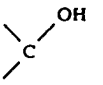
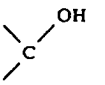
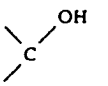


Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7A-1	CH_2Cl	C_2H_5	H	F	H		4	228–229° C. (THF/hexane)
7A-2	CH_2Cl	C_2H_5	β-CH_3	F	H		1,4	220–221° C. (THF/hexane)
7A-3	CH_2Cl	C_2H_5	α-CH_3	F	H		1,4	230–235° C. (THF/hexane)
7A-4	CH_2Cl	C_2H_5	H	H	H		1,4	220.5–223.5° C. (THF/hexane)

-continued

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7A-5	CH_2Cl	iso-C_3H_7	H	H	H		1,4	197–198° C. (THF/hexane)
7A-6	CH_2Cl	C_2H_5	H	F	H		1,4	245–248° C. (THF/hexane)
7A-7	CH_2Cl	iso-C_3H_7	α-CH_3	F	H		1,4	184.5–186° C. (THF/hexane)
7A-8	CH_2Cl	iso-C_3H_7	β-CH_3	F	H		1,4	174–175.5° C. (THF)
7A-9	CH_2Cl	iso-C_4H_9	H	H	H		4	140–141° C. (THF/isopropyl ether)
7A-10	CH_2Cl		H	H	H		4	148–150° C. (isopropyl ether hexane)
7A-11	CH_2Cl	n-C_3H_7	H	H	H		4	181–182° C. (THF/hexane)
7A-12	CH_2Cl	n-C_3H_7	α-CH_3	F	H		1,4	176–176.5° C. (THF/hexane)
7A-13	CH_3	iso-C_3H_7	H	H	H		4	211.5–213.5° C. (THF/hexane)
7A-14	$CH_2OC_2H_5$	iso-C_3H_7	H	H	H		4	137–138° C. (THF/hexane)
7A-15	CH_2Cl		H	H	H		4	182–183° C. (ethanol)
7A-16*	CH_3 | CHCl	iso-C_3H_7	H	H	H		4	181–182.5° C. (THF/hexane)
	CH_3 | CHCl	iso-C_3H_7	H	H	H		4	199–200° C. (THF/hexane)
7A-17	$CH_2CO_2C_2H_5$	iso-C_3H_7	H	H	H		4	73–74° C. (isopropyl ether)

-continued

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7A-18*	CH_3 | CHCl	iso-C_3H_7	β-CH_3	F	H		1,4	167.5–169° C. (THF/hexane)
	CH_3 | CHCl	iso-C_3H_7	β-CH_3	F	H		1,4	163–164° C. (THF/hexane)
7A-19	CH_2Cl	iso-C_3H_7	β-CH_3	F	H		1,4	200–201° C. (THF/isopropyl ether)
7A-20	CH_2Cl	C_2H_5	α-CH_3	F	H		1,4	138–140° C. (THF/isopropyl ether)
7A-21	CH_2Cl	CH_3	α-CH_3	F	H		1,4	260–263° C. (THF/hexane)
7A-22	CH_2F	iso-C_3H_7	H	H	H		4	207.5–210° C. (THF/hexane)
7A-23	CH_2Cl	n-C_5H_{11}	α-CH_3	F	H		1,4	176–177° C. (THF/hexane)
7A-24	CH_2Cl	C_2H_5		H	F		1,4	153–154° C. (THF/hexane)
7A-25	CH_2F	C_2H_5	α-CH_3	F	H		1,4	239–240.5° C. (THF/hexane)
7A-26	CH_2OCOCH_3	C_2H_5	H	H	H		4	NMR ($CDCl_3$) δ5.76(s,2, $OC\underline{H_2}O$), 2.01 (s,3, $COC\underline{H_3}$)
7A-27	CH_2Cl	C_2H_5	α-CH_3	F	F		1,4	195–197° C. (THF/hexane)
7A-28	CH_2CH_2Cl	C_2H_5	α-CH_3	F	H		1,4	243–245° C. (THF/hexane)
7A-29	CH_3	C_2H_5	α-CH_3	F	H		1,4	258.5–262.5° C. (THF/hexane)

-continued

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7A-30	CH_2CH_2Cl	iso-C_3H_7	H	H	H		4	188.5–189.5° C. (THF/hexane)

*diastereomers

The foregoing compounds can be named as follows:

7A-1: chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxyandrost-4-en-3-one-17β-carboxylate

7A-2: chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-3: chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-4: chloromethyl 17β-ethoxycarbonyloxy-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate

7A-5: chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7A-6: chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate

7A-7: chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-8: chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-9: chloromethyl 11β-hydroxy-17α-isobutoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate

7A-10: chloromethyl 17α-cyclohexyloxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate

7A-11: chloromethyl 11β-hydroxy-17α-propoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate

7A-12: chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7A-13: methyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate

7A-14: ethoxymethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate

7A-15: chloromethyl 17α-benzyloxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate

7A-16: 1-chloroethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate

7A-17: ethoxycarbonylmethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17βcarboxylate

7A-18: 1-chloroethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-19: chloromethyl 9α-fluoro-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3,11-dione-17-carboxylate

7A-20: chloromethyl 9α-fluoro-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3,11-dione-17-carboxylate

7A-21: chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrost-1,4-dien-3-one-17β-carboxylate

7A-22: fluoromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate

7A-23: chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7A-24: chloromethyl 16α,17α-di(ethoxycarbonyloxy)-6α-fluoro-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate

7A-25: fluoromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-26: acetoxymethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate

7A-27: chloromethyl 17α-ethoxycarbonyloxy-6α,9α-difluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

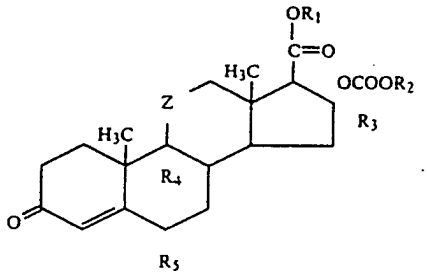
7A-28: 2-chloroethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-29: methyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7A-30: 2-chloroethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate

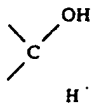
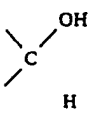
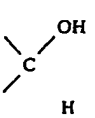
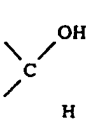
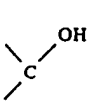
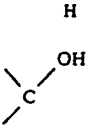
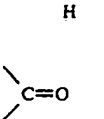
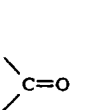
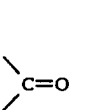
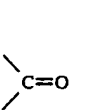
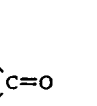
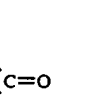
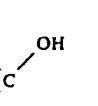
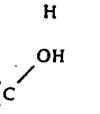
EXAMPLE 7B

Following the general procedure of Examples 3 or 4 and substituting therein the appropriate reactants affords the following comppounds:

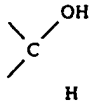
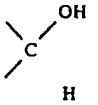
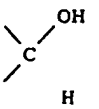
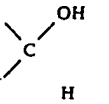
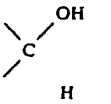
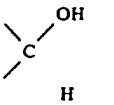
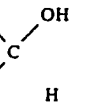
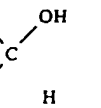
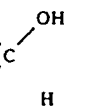
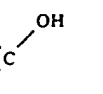
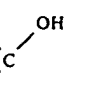


Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-1	C_2H_5	C_2H_5	H	H	H		4

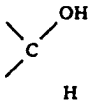
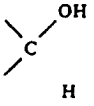
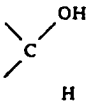
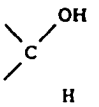
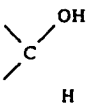
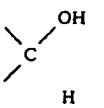
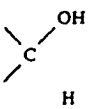
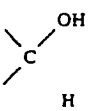
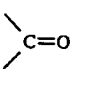
-continued

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-2	C_4H_9	$CH_2C_6H_5$	H	H	H		4
7B-3	$CH_2COOC_2H_5$	C_2H_5	H	H	H		4
7B-4	CH_2OCOCH_3	C_2H_5	H	H	H		4
7B-5	CH_2Cl	C_6H_5	H	H	H		4
7B-6	CH_2Cl		H	H	H		4
7B-7	CH_2Cl	CH_2SCH_3	H	H	H		4
7B-8	C_4H_9	C_2H_5	H	H	H		4
7B-9	CH_2Cl	CH_3	H	H	H		4
7B-10	CH_2Cl	C_2H_5	H	H	H		4
7B-11	CH_2SCH_3	C_2H_5	H	H	H		4
7B-12	$CH_2SO_2CH_3$	C_2H_5	H	H	H		4
7B-13	CH_2SOCH_3	C_2H_5	H	H	H		4
7B-14	CH_2Cl	CH_3	H	F	H		4
7B-15	CH_2SCH_3	C_2H_5	H	F	H		4

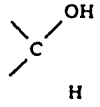
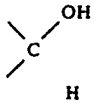
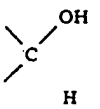
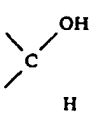
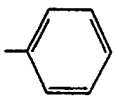
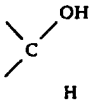
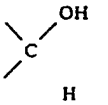
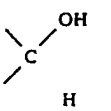
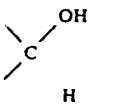
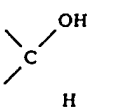
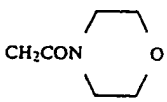
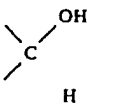
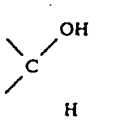
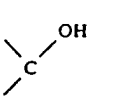
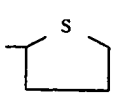
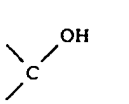
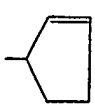
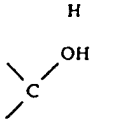
-continued

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-16	$CH_2SO_2CH_3$	C_2H_5	H	F	H		4
7B-17	CH_2SCH_3	C_2H_5	β-CH_3	F	H		1,4
7B-18	$CH_2SO_2CH_3$	C_2H_5	β-CH_3	F	H		1,4
7B-19	CH_2Cl	C_2H_5	H	H	Cl		1,4
7B-20	CH_2SCH_3	C_2H_5	H	H	Cl		1,4
7B-21	$CH_2SO_2CH_3$	C_2H_5	H	H	Cl		1,4
7B-22	CH_2SCH_3	C_2H_5	α-CH_3	F	H		1,4
7B-23	$CH_2SO_2CH_3$	C_2H_5	α-CH_3	F	H		1,4
7B-24	CH_2Cl	C_2H_5	α-CH_3	F	F		1,4
7B-25	CH_2SCH_3	C_2H_5	α-CH_3	F	F		1,4
7B-26	$CH_2SO_2CH_3$	C_2H_5	α-CH_3	F	F		1,4
7B-27	CH_2Cl	C_2H_5	H	H	F		1,4
7B-28	CH_2SCH_3	C_2H_5	H	H	F		1,4
7B-29	$CH_2SO_2CH_3$	C_2H_5	H	H	F		1,4

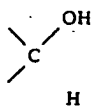
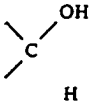
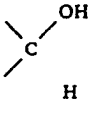
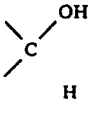
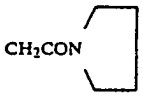
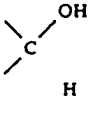
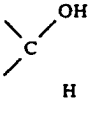
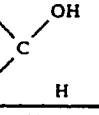
-continued

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-30	CH_2Cl	C_2H_5	β-CH_3	H	H		1,4
7B-31	CH_2SCH_3	C_2H_5	β-CH_3	H	H		1,4
7B-32	$CH_2SO_2CH_3$	C_2H_5	β-CH_3	H	H		1,4
7B-33	CH_2Cl	C_2H_5	H	H	CH_3		1,4
7B-34	CH_2SCH_3	C_2H_5	H	H	CH_3		1,4
7B-35	$CH_2SO_2CH_3$	C_2H_5	H	H	CH_3		1,4
7B-36	CH_2Cl	C_2H_5	α-CH_3	H	F		1,4
7B-37	CH_2SCH_3	C_2H_5	α-CH_3	H	F		1,4
7B-38	$CH_2SO_2CH_3$	C_2H_5	α-CH_3	H	F		1,4
7B-39	CH_2SCH_3	C_2H_5	H	H	H		1,4
7B-40	$CH_2SO_2CH_3$	C_2H_5	H	H	H		1,4
7B-41	CH_2Cl	C_2H_5	H	H	H		1,4
7B-42	CH_2SCH_3	C_2H_5	H	H	H		1,4
7B-43	$CH_2SO_2CH_3$	C_2H_5	H	H	H		1,4

-continued

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-44	CH_2Cl	C_2H_5	α-$OCOOC_2H_5$	F	H		1,4
7B-45	CH_2SCH_3	C_2H_5	α-$OCOOC_2H_5$	F	H		1,4
7B-46	$CH_2SO_2CH_3$	C_2H_5	α-$OCOOC_2H_5$	F	H		1,4
7B-47	CH_2Cl	C_2H_5	α-OH	H	F		1,4
7B-48	CH_2Cl		α-CH_3	F	H		1,4
7B-49	CH_2Cl	CH_2CH_2Cl	α-CH_3	F	H		1,4
7B-50	CH_3	CH_2Cl	α-CH_3	F	H		1,4
7B-51	C_4H_9	CH_2CCl_3	H	H	H		4
7B-52	$CH_2CON(C_2H_5)_2$	C_2H_5	H	H	H		4
7B-53		CH_3	H	H	H		4
7B-54	C_6H_5	C_2H_5	H	H	H		4
7B-55	$CH_2C_6H_5$	CH_3	H	H	H		4
7B-56		C_2H_5	H	H	H		4
7B-57	CH_2Cl		H	H	H		4

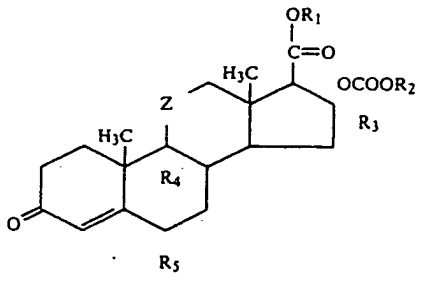
-continued

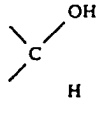
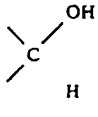
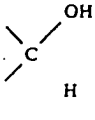
Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ
7B-58	CH_2Cl	$CH{=}CH_2$	H	H	H		4
7B-59	CH_2Cl	CH_2OCH_3	H	H	H		4
7B-60	CH_2Cl	$CH_2CH_2NHCOCH_3$	H	H	H		4
7B-61	CH_2Cl	$CH_2CH_2OCOCH_3$	H	H	H		4
7B-62		C_2H_5	H	H	H		4
7B-63	CH_2Cl	$CH_2SO_2CH_3$*	H	H	H		4
7B-64	CH_2Cl	CH_2SOCH_3*	H	H	H		4

*prepared from Example 6B-24 and 6B-25 respectively by reaction with $ClCH_2I$, or from Example 7B-7 by reaction with m-chloroperbenzoic acid.

EXAMPLE 7C

Following the general procedure of Example 3 and substituting therein the appropriate reactants affords the following compounds:



Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7C-1	$-CH_2Cl$	$-CH(CH_3)_2$	α-CH_3	F	F		1,4	222-224° C. (THF/hexane)
7C-2	$-CH_2Cl$	$-CH_2CH_2CH_3$	α-CH_3	F	F		1,4	180.5-181.5° C. (THF/hexane)
7C-3	$-CH_2F$	$-CH_2CH_2CH_3$	α-CH_3	F	H		1,4	165-165.5° C. (THF/hexane)

-continued

Compound No.	R_1	R_2	R_3	R_4	R_5	Z	Δ	m.p.
7C-4	$-CH_2CH_2Cl$	$-CH(CH_3)_2$	H	H	H	OH, H	1,4	188.5–189.5° C. (THF/hexane)
7C-5	$-CH_3$	$-CH_2CH_2Cl$	α-CH_3	F	H	OH, H	1,4	223–227° C. (isopropanol)
7C-6	$-CH_2Cl$	$-C_2H_5$	α-CH_3	H	F	OH, H	1,4	153.5–154.5° C. (THF/n-hexane)
7C-7	$-CH_2Cl$	$-(CH_2)_2CH_3$	α-CH_3	H	F	OH, H	1,4	98.5–99.5° C. (ethyl acetate/n-hexane)
7C-8	$-CH_2Cl$	$-CH(CH_3)_2$	α-CH_3	H	F	OH, H	1,4	124.5–126° C. (ethyl acetate/n-hexane)
7C-9	$-CH_2Cl$	$-(CH_2)_2CH_3$	H	H	H	OH, H	1,4	180.5–181.5° C. (THF/n-hexane)
7C-10	$-CH_2Cl$	$-CH_3$	H	H	H	OH, H	1,4	235–237° C. (THF/n-hexane)
7C-11	$-CH_2Cl$	$-CH_3$	α-CH_3	H	F	OH, H	1,4	244.5–245.5° C. (THF/n-hexane)
7C-12	$-CH_2Cl$	$-CH_3$	β-CH_3	F	H	OH, H	1,4	236–236.5° C. (THF/n-hexane)
7C-13	$-CH_2Cl$	$-CH_2CH_2CH_3$	β-CH_3	F	H	OH, H	1,4	183.5–184° C. (THF/n-hexane)

The foregoing compounds can be named as follows:

7C-1: chloromethyl 6α,9α-difluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-2: chloromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-3: fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-4: 2-chloroethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-5: methyl 17α-(2-chloroethoxy)carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-6: chloromethyl 17α-ethoxycarbonyloxy-6α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-7: chloromethyl 6α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-8: chloromethyl 6α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-9: chloromethyl 11β-hydroxy-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-10: chloromethyl 11β-hydroxy-17α-methoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

7C-11: chloromethyl 6α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-12: chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate

7C-13: chloromethyl 9α-fluoro-11β-hydroxy-16β-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

EXAMPLE 8

An equivalent quantity of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid is substituted for the 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid starting material employed in Example 3, and the procedure of the first paragraph of that example is substantially repeated. There are thus obtained, as the intermediate salt, sodium 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate, melting at 184°–186° C. (recrystallization from tetrahydrofuran-ether-hexane).

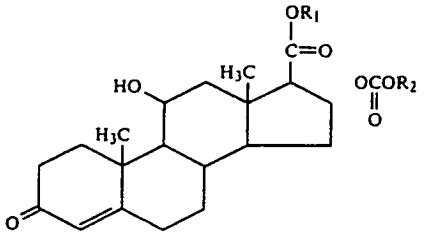
EXAMPLE 9

An equivalent quantity of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid is substituted for the 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid starting material employed in Example 4, and the procedure of the first paragraph of that example is substantially repeated. There are thus obtained, as the intermediate salt, sodium 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate, and, as the final product, methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate

Substitution of an equivalent quantity of methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate for the methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate used in the second paragraph of Example 4 and substantial repetition of the procedure there detailed affords methylsulfonylmethyl 11α,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate.

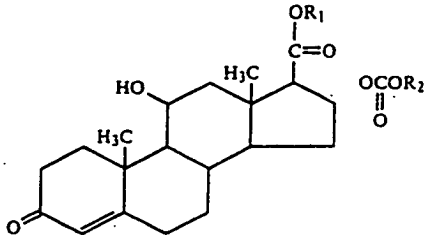
EXAMPLE 10A

The procedure of each paragraph of Example 2 is substantially repeated, substituting an equivalent quantity of each of the following starting materials for the steroids employed therein: chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate; and methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate. The following soft anti-inflammatory agents of formula (I) are obtained:



Compound No.	R_1	R_2	m.p.
10A-1	CH_2Cl	CH_3	171–173° C.
10A-2	CH_2Cl	C_2H_5	197–200° C. (THF/hexane)
10A-3	CH_2SCH_3	C_2H_5	137.5–138° C. (ether/hexane)
10A-4	CH_2Cl	C_4H_9	99.5–102° C.

-continued

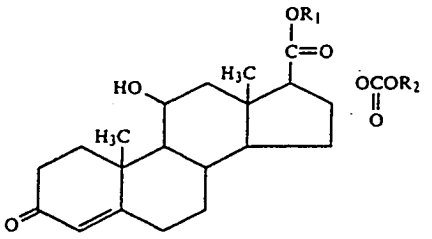


Compound No.	R_1	R_2	m.p.
10A-5	CH_2Cl	iso-C_3H_7	(THF/hexane) 183.5–184.5° C.
10A-6*	CH_2Cl	iso-C_4H_9	(THF/hexane) 140–141° C. (THF/isopropyl ether)

*utilizing isobutyl chloroformate as the alkyl chloroformate reactant

EXAMPLE 10B

The procedure of each paragraph of Example 2 is substantially repeated, substituting an equivalent quantity of each of the following starting materials for the steroids employed therein: methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate; and methylfulfonylmethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate. The following soft anti-inflammatory agents of formula (I) are obtained.

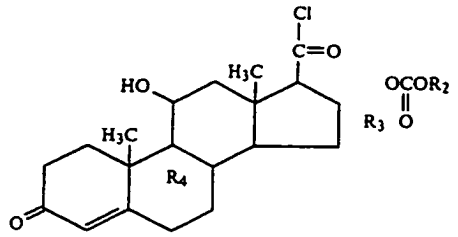


Compound No.	R_1	R_2
10B-1	CH_2SCH_3	CH_3
10B-2	CH_2SCH_3	C_4H_9
10B-3	CH_2SCH_3	i-C_3H_7
10B-4	$CH_2SO_2CH_3$	CH_3
10B-5	$CH_2SO_2CH_3$	C_2H_5
10B-6	$CH_2SO_2CH_3$	C_4H_9
10B-7	$CH_2SO_2CH_3$	i-C_3H_7

Other representative species, e.g. compounds of Examples 7A and 7B, can likewise be prepared according to the procedures of Examples 8 through 10.

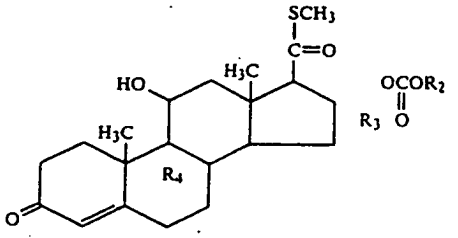
EXAMPLE 11

The products of Example 2 and Example 6A-4 are each allowed to react, first with diethylchlorophosphate and then with CH_3SNa in chloroform for approximately 6 hours. The following intermediates are obtained in the first step:



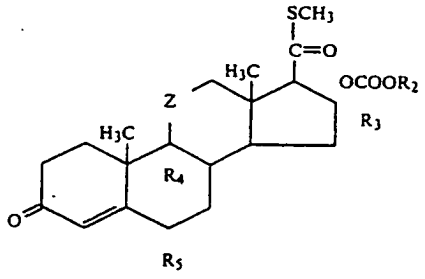
R_2	R_3	R_4	Δ
CH_3	H	H	4
C_2H_5	H	H	4
C_4H_9	H	H	4
i-C_3H_7	H	H	4
C_2H_5	α-CH_3	F	1,4

and the following compounds of formula (I) are obtained in the second step:



R_2	R_3	R_4	Δ
CH_3	H	H	4
C_2H_5	H	H	4
C_4H_9	H	H	4
i-C_3H_7	H	H	4
C_2H_5	α-CH_3	F	1,4

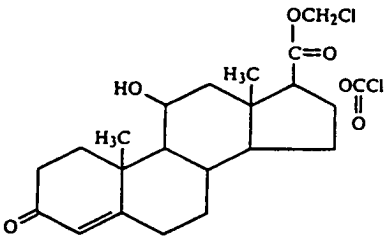
When the remaining products of Example 6A and those of Example 6B are treated according to the above procedure, the corresponding compounds of the formula



wherein the various structural parameters represented by R_2, R_3, R_4, R_5, Z and the dotted line are identical to those of compounds 6A1-6A3, 6A5-6A11, and 6B1-6B25 of Examples 6A and 6B are obtained.

EXAMPLE 12

Chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate (0.01 mol) is dissolved in toluene (100 milliliters) and the solution is cooled to approximately 0° C. Phosgene is then bubbled into the solution, while maintaining the reaction mixture at low temperature, until the reaction is complete (approximately 2 hours). The solvent and excess phosgene are removed by evaporation to leave the crude 17α-chlorocarbonyloxy compound of the formula



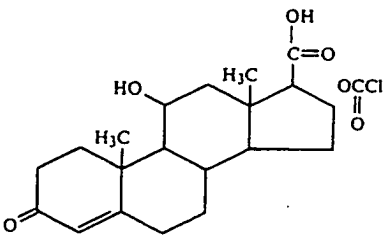
The intermediate (0.01 mol) obtained above is then combined with ethanol (0.02 mol) containing 2,6-dimethylpyridine (0.01 mol) and allowed to react at room temperature for 6 hours. At the end of that time, the desired chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate is isolated from the reaction mixture. The compound melts at 197°-200° C., after crystallization.

Substitution of an equivalent quantity of methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate for the chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate used above and substantial repetition of the foregoing procedure affords methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 133°-136° C., after crystallization. That compound can then, if desired, be converted to the corresponding sulfonyl or sulfinyl compound as described in Example 4.

Other representative species, e.g., the compounds of Example 3, paragraphs 1, 3, 4 and 5, and the compounds of Examples 7A and 7B can be prepared in like manner from reaction of the corresponding 17α-hydroxy 17β-carboxylates with the appropriate alcohols, including, when appropriate, subsequent treatment with m-chloroperoxybenzoic acid as in Example 4.

EXAMPLE 13

The procedure of the first paragraph of Example 12 is repeated, except that an equivalent quantity of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid is used in place of the chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate. The crude intermediate thus obtained has the formula



That intermediate is then subjected to the procedure of the second paragraph of Example 12, to afford 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, identical to the product of Example 2, paragraph 2.

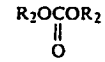
The other compounds of Examples 2, 6A and 6B can be prepared using the same general procedure.

EXAMPLE 14

Chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate (0.02 mol) is combined with diethylcarbonate (0.2 mol) containing 20 mg of p-toluenesulfonic acid. The reaction mixture is maintained at room temperature for 4 hours, then heated to about 80° to 85° C.; the remaining ethanol which forms is removed by distillation under reduced pressure. Obtained as the residue is crude chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 197°–200° C., after crystallization.

Substitution of an equivalent quantity of methylthiomethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate for the chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate used above and substantial repetition of the foregoing procedure affords methylthiomethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 133°–136° C. That compound can then, if desired, be converted to the corresponding sulfonyl or sulfinyl compound as described in Example 4.

Other representative species, e.g., the compounds of Example 3, paragraphs, 1, 3, 4 and 5, and the compounds of Examples 7A and 7B, can be prepared in like manner from reaction of the corresponding 17α-hydroxy-17β-carboxylates with the appropriate carbonates of the type



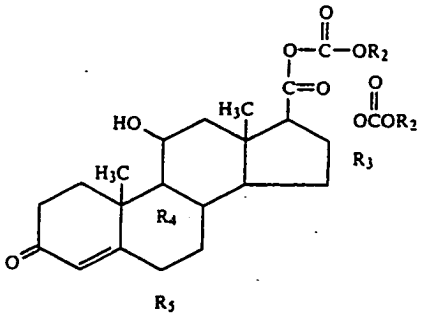
(including, when appropriate, subsequent treatment with m-chloroperoxybenzoic acid as in Example 4).

EXAMPLE 15

To a solution of 8.7 grams of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid and 9.6 milliliters of triethylamine in 100 milliliters of dry dichloromethane, is added 10 grams of ethyl chloroformate, dropwise at 0° to 5° C. The reaction mixture is gradually allowed to warm to room temperature and the insoluble material is removed by filtration. The filtrate is washed successively with 3% aqueous sodium bicarbonate, 1% hydrochloric acid, and water, then is dried over anhydrous magnesium sulfate. The solvent is concentrated under reduced pressure and the residue is crystallized to give 10.5 grams of ethoxycarbonyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, melting at 158°–159° C.

EXAMPLE 16

Following the general method described in Example 15 and substituting therein the appropriate reactants affords the following additional compounds:



Compound No.	R_2	R_3	R_4	R_5	Δ	melting point
16-A	$-CH_2CH_3$	H	F	H	4	110–111° C. (THF-isopropyl ether)
16-B	iso-C_3H_7	H	H	H	4	200–203° C.
16-C	$-CH_2CH_2CH_3$	H	H	H	4	142–143° C. (THF)

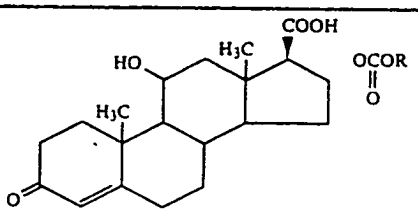
EXAMPLE 17

To a solution of 9.8 grams of ethoxycarbonyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate in 100 milliliters of tetrahydrofuran and 120 milliliters of ethanol are added 42 milliliteres of 5% aqueous sodium becarbonate. The mixture is stirred at room temperature for about 30 hours and adjusted to pH 2 to 3 by adding 1N hydrochloric acid. The insoluble material is isolated by filtration. Recrystallization from a mixture of tetrahydrofuran and n-hexane gives 6 grams of 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid having a melting point of 192°–195° C.

The compound obtained in Example 2, first paragraph, and the compounds of Example 6A can be prepared, following the same procedure as above and substituting therein appropriate reactants.

EXAMPLE 18

Following the general method described in Example 17 and substituting therein the appropriate reactants affords the following compounds:



Compound No.	R	melting point
18-A		144.5–146.5° C. (THF/hexane)
18-B	$-(CH_2)_3CH_3$	164–166° C. (THF/hexane)

EXAMPLE 19

To a solution of 8.7 grams of 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylic acid and 10 grams of triethylamine in 100 milliliters of dichloromethane, a

solution of 13.2 grams of n-propyl chloroformate in 20 milliliters of dichloromethane is added dropwise over 1–1.5 hours with ice-cooling. The reaction mixture is allowed to warm to room temperature over a 2 hour period, then is washed successively with 3% aqueous sodium bicarbonate, 1N hydrochloric acid, and water and dried over anhydrous sodium sulfate. The solvent is concentrated under reduced pressure. Crystallization from a mixture of ether and n-hexane gives 10.5 grams of propoxycarbonyl 11β-hydroxy-17α-propoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, which is dissolved in 40 milliliters of pyridine. To that solution, 300 milliliters of water are added dropwise over a 1 to 1.5 hour period. The mixture is stirred for one hour and adjusted to pH 2 to 2.5 by adding concentrated hydrochloric acid with ice-cooling. The mixture is then extracted with chloroform, washed successively with 1N hydrochloric acid and water, and then dried over sodium sulfate. The solvent is concentrated under reduced pressure, and the residue is recrystallized from a mixture of acetone and tetrahydrofuran to give 7.7 grams of 11β-hydroxy-17α-propoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid, melting at 156°–157° C.

EXAMPLE 20

Following the general procedure detailed in Example 19, but utilizing the appropriate starting materials and reaction conditions, affords the remaining compounds of Example 6A.

EXAMPLE 21

Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate (2 grams) is dissolved in anhydrous dichloromethane (200 milliliters) and pyridinium chlorochromate (3.5 grams) is added at room temperature, with stirring. The resultant mixture is stirred for 24 hours, then the solvent is concentrated under reduced pressure at about 10° to 20° C. The residue is subjected to column chromatography on silica gel (Kiesel gel 60), using chloroform as an eluting solvent, followed by recrystallization from a mixture of tetrahydrofuran and isopropyl ether to give chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-16α-methylandrosta-1,4-dien-3,11-dione-17β-carboxylate, in the yield of 1.7 grams, melting at 138°–140° C.

EXAMPLE 22

By a method similar to that described in Example 21, there is obtained chloromethyl 9α-fluoro-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3,11-dione-17β-carboxylate, melting at 200°–201° C.

EXAMPLE 23

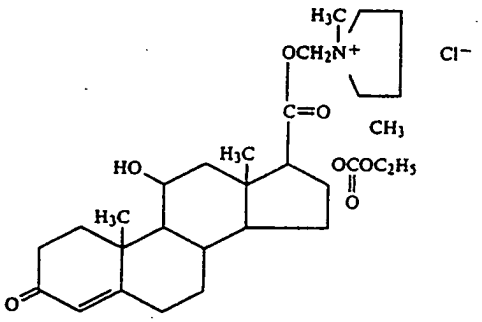
Utilizing the general procedure of Example 3, but substituting the appropriate reactants therein, affords methyl 17α-(2-chloroethoxy)carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate. That product, after recrystallization from isopropanol, melts at 223°–227° C.

EXAMPLE 24

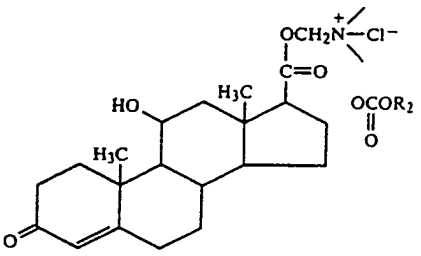
In the same general manner as in Example 3, there is obtained 2-chloroethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate. That product, after recrystallization from tetrahydrofuran-hexane, melts at 243°–245° C.

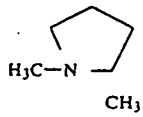
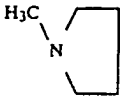
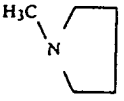
EXAMPLE 25

Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate (0.01 mol) and 1,2-dikmethylpyrrolidine (0.01 mol) are dissolved in acetonitrile (80 milliliters), and heated to the reflux temperature. The reaction mixture is maintained at that temperature, with stirring, for approximately 4 hours. About 65 ml of acetonitrile are removed; then, the mixture is cooled to room temperature and excess ethyl ether is added to cause precipitation. The precipitate is separated by filtration, washed, and dried in vacuo, thus affording the desired quaternary ammonium salt of the formula

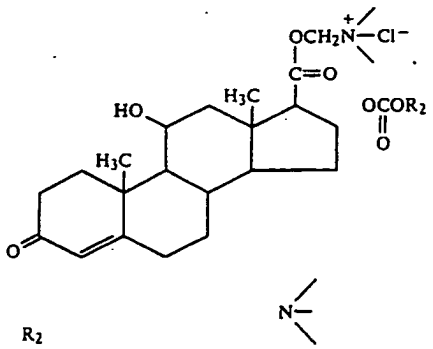


In analogous fashion, use of the appropriate steroidal and amine starting materials in the foregoing general procedure affords the following additional quaternary ammonium salts of the invention



R_2	N
CH_3	
$i\text{-}C_3H_7$	$N(C_2H_5)_3$
C_4H_9	
C_2H_5	

-continued



R_2
C_2H_5
C_2H_5
C_2H_5

EXAMPLE 26

Ointment		
Compound of formula (I), e.g. chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate or chloromethyl 11β-hydroxy-17α-isopropoxycarbonyl-oxyandrost-4-en-3-one-17β-carboxylate	0.2%	w/w
Liquid paraffin	10.0%	w/w
White soft paraffin	89.8%	w/w
Aphthous Ulcer Pellet		
Compound of formula (I), as above	0.25	mg
Lactose	69.90	mg
Acacia	3.00	mg
Magnesium stearate	0.75	mg
Retention Enema		
Compound of formula (I), as above	0.001%	w/v
Tween 80	0.05%	w/v
Ethanol	0.015%	w/v
Propylparaben	0.02%	w/v
Methylparaben	0.08%	w/v
Distilled water	q.s. 100 volumes	
Eye Drops		
Compound of formula (I), as above	0.1%	w/v
Tween 80	2.5%	w/v
Ethanol	0.75%	w/v
Benalkonium chloride	0.02%	w/v
Phenyl ethanol	0.25%	w/v
Sodium chloride	0.60%	w/v
Water for injection	q.s. 100 volumes	

EXAMPLE 27

Ointment		
Compound of formula (I), e.g. chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate or chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.025%	w/w
Liquid paraffin	10.175%	w/w
White soft paraffin	89.8%	w/w
Aphthous Ulcer Pellet		
Compound of formula (I), e.g. chloromethyl 9α-fluoro-11α-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate or chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.1	mg
Lactose	69.90	mg
Acacia	3.00	mg
Magnesium stearate	0.75	mg
Retention Enema		
Compound of formula (I), e.g. chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate or chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate	0.001%	w/v
Tween 80	0.05%	w/v
Ethanol	0.015%	w/v
Propylparaben	0.02%	w/v
Methylparaben	0.08%	w/v
Distilled water	q.s. 100 volumes	
Eye Drops		
Compound of formula (I), e.g. chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxy-carbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate or chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxy-carbonyloxy-16α-methyl-androsta-1,4-dien-3-one-17β-carboxylate	0.025%	w/v
Tween 80	2.5%	w/v
Ethanol	0.75%	w/v
Benzalkonium chloride	0.02%	w/v
Phenyl ethanol	0.25%	w/v
Sodium chloride	0.60%	w/v
Water for injection	q.s. 100 volumes	

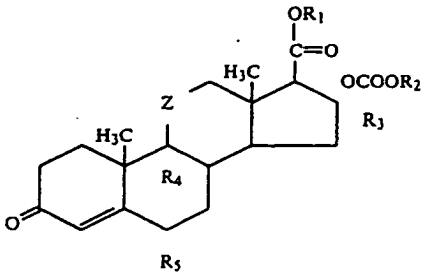
EXAMPLE 28

To a solution of 3 grams of chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate in 100 ml of acetonitrile, 7.9 grams of AgF (a 10:1 molar ratio of AgF to steriod) are added, and the mixture is stirred at room temperature for 12 days while shading the reaction system for light. Thereafter, the reaction mixture is filtered, and the solid on the filter is fully washed with ethyl acetate. The filtrate and the ethyl acetate solution are combined, and the mixture is washed with water and a saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The solvents are distilled off, giving 2 grams of crude crystalline product. The product is subjected to preparative thin-layer chromatography (Silica

Gel 60F254, Merck), using a mixture of chloroform and methanol (15:1) as an eluting solvent. Then the product is recrystallized from a mixture of tetrahydrofuran and n-hexane to give 180 mg of fluoromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate as colorless needles, melting at 207.5°–210° C.

EXAMPLE 29

Following the general procedure of Example 28 and substituting therein the appropriate reactants affords the following compounds:



The foregoing compounds can be named as follows:

29-1: fluoromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate

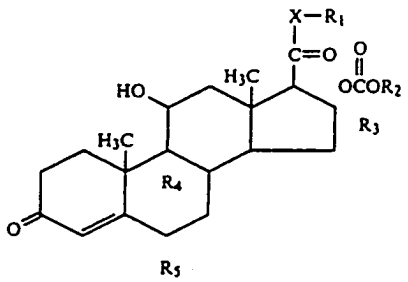
29-2: fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate

From the foregoing description, one of ordinary skill in the art can readily ascertain the essential characteristics of the present invention and, without departing from the spirit and scope thereof, can make various changes in and/or modifications of the invention to adapt it to various usages and conditions. As such, these changes and/or modifications are properly, equitably and intended to be within the full range of equivalence of the following claims.

What is claimed is:

1. A compound selected from the group consisting of:

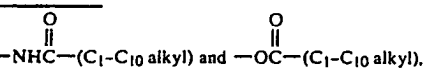
(a) a compound of the formula



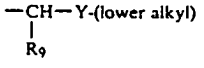
(I)

wherein:

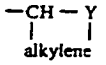
R_1 is C_1–C_{10} alkyl; C_2–C_{10} (monohydroxy or polyhydroxy)alkyl; C_1–C_{10} (monohalo or polyhalo)alkyl; or $—CH_2COOR_6$ wherein R_6 is unsubstituted or substituted C_1–C_{10} alkyl; C_3–C_8 cycloalkyl, C_3–C_8 cycloalkenyl or C_2–C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,



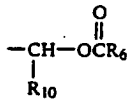
or R_6 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carabamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R_1 is $—CH_2CONR_7R_8$ wherein R_7 and R_8, which can be the same or different, are each hydrogen, lower alkyl, C_3–C_8 cycloalkyl, phenyl or benzyl, or R_7 and R_8 are combined such that $—NR_7R_8$ represents the residue of a saturated monocyclic secondary amine; or R_1 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to R_6; or R_1 is



wherein Y is —S—, —SO—, $—SO_2—$ or —O— and R_9 is hydrogen, lower alkyl or phenyl, or R_9 and the lower alkyl group adjacent to Y are combined so that R_1 is a cyclic system of the type

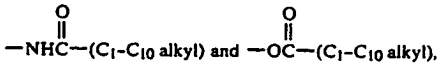


wherein Y is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms; or R_1 is



wherein R_6 is defined as hereinabove and R_{10} is hydrogen, lower alkyl, phenyl or halophenyl;

R_2 is unsubstituted or substituted C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl or C_2-C_{10} alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,



or R_2 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxycarbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl;

R_3 is hydrogen, α-hydroxy, β-hydroxy, α-methyl, β-methyl, $=CH_2$, or α- or

wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen, fluoro or chloro;

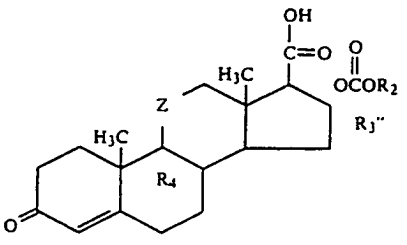
R_5 is hydrogen, fluoro, chloro or methyl;

X is —O— or —S—;

and the dotted line in ring A indicates that the 1,2 linkage is saturated or unsaturated;

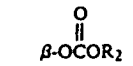
(b) a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group;

(c) a compound of the formula



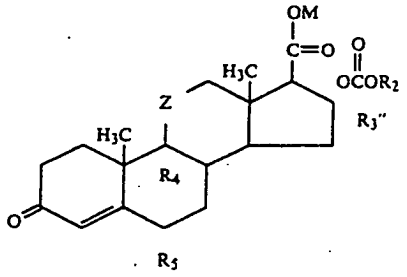
(III)

wherein R_2, R_4, R_5, and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β-hydroxymethylene and R_3" is hydrogen, α-methyl, β-methyl, $=CH_2$ or α- or



wherein R_2 is identical to R_2 above;

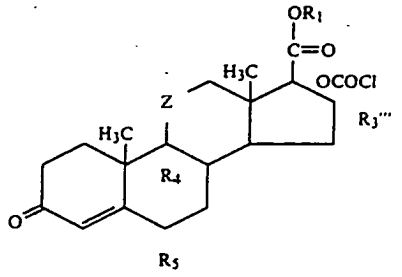
(d) a compound of the formula



(IV)

wherein M is alkali metal, thallium, alkaline earth metal/2 or NH_4 and R_2, R_3", R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

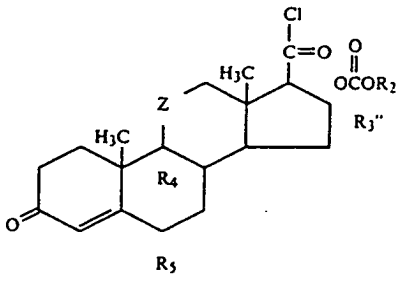
(e) a compound of the formula



(VII)

wherein R_3''' is hydrogen, α-methyl, β-methyl, α-OCOCl or β-OCOCl, and R_1, R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

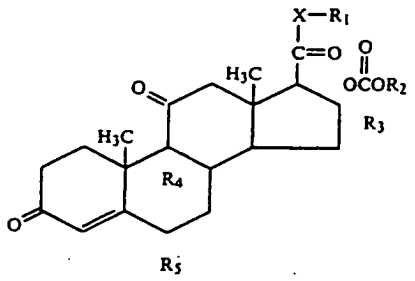
(f) a compound of the formula



(VIII)

wherein R_2, R_3", R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above; and

(g) a compound of the formula

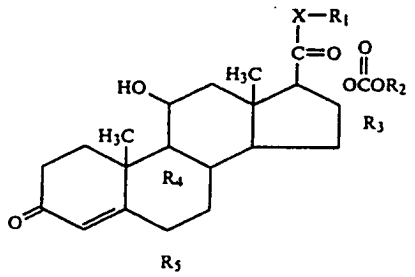


(IX)

wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in ring A are as defined in (a) above.

2. A compound selected from the group consisting of:

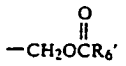
(a) a compound of the formula



(I)

wherein:

R_1 is C_1–C_6 alkyl; C_1–C_6 (monohalo or polyhalo)alkyl; —CH_2COOR_6 wherein R_6 is C_1–C_6 alkyl; —CH_2—Y—(C_1–C_6 alkyl) wherein Y is —S—, —SO—, —SO_2— or —O—; or



wherein R_6' is C_1–C_6 or phenyl;

R_2 is C_1–C_6 alkyl, C_3–C_8 cycloalkyl, phenyl, benzyl or C_1–C_6 (monohalo or polyhalo)alkyl;

R_3 is hydrogen, α-hydroxy, β-methyl, β-methyl or

wherein R_2 is identical to R_2 as defined hereinabove;

R_4 is hydrogen or fluoro;

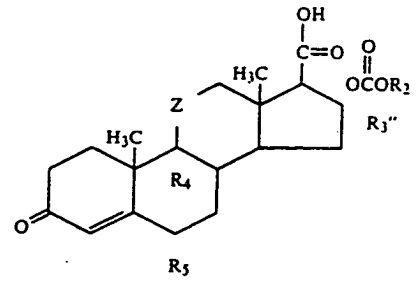
R_5 is hydrogen or fluoro;

X is —O—;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated;

(b) a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group;

(c) a compound of the formula

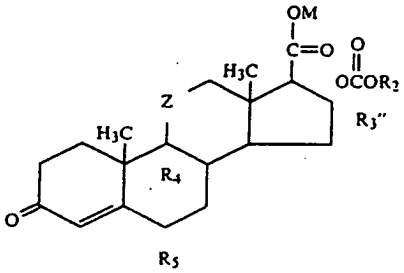


(III)

wherein R_2, R_4, R_5 and the dotted line in ring A are as defined in (a) above, Z is carbonyl or β-hydroxymethylene and R_3'' is hydrogen, α-methyl, β-methyl or

wherein R_2 is identical to R_2 above;

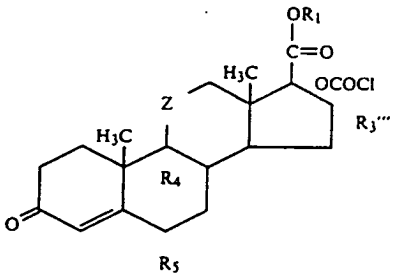
(d) a compound of the formula



(IV)

wherein M is alkali metal, thallium, alkaline earth metal/2 or NH_4 and R_2, R_3'', R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

(e) a compound of the formula

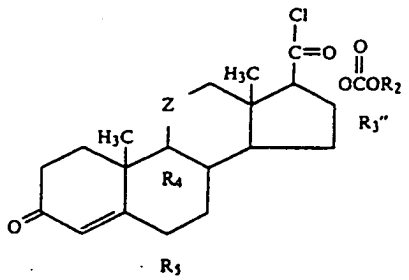


(VII)

wherein R_3''' is hydrogen, α-methyl, β-methyl or α-OCOCl, and R_1, R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above;

(f) a compound of the formula

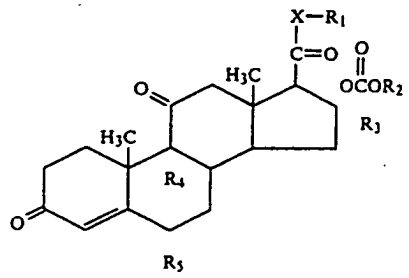
(VIII)



wherein R_2, R_3'', R_4, R_5, Z and the dotted line in ring A are as defined in (a) and (c) above; and

(g) a compound of the formula

(IX)



wherein R_1, R_2, R_3, R_4, R_5, X and the dotted line in ring A are as defined in (a) above.

3. A compound of claim 1 or 2, said compound having the structural formula (I).

4. A compound of claim 1 or 2, said compound being a quaternary ammonium salt of a compound of formula (I) wherein at least one of R_1 and R_2 is a halo-substituted alkyl group.

5. A compound of claim 1 or 2, said compound having the structural formula (III).

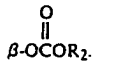
6. A compound of claim 1 or 2, said compound having the structural formula (IV).

7. A compound of claim 1 or 2, said compound having the structural formula (VII).

8. A compound of claim 1 or 2, said compound having the structural formula (VIII).

9. A compound of claim 1 or 2, said compound having the structural formula (IX).

10. A compound of claim 1, said compound having the structural formula (I) wherein R_3 is hydrogen, α-methyl, β-methyl, $=CH_2$ or α- or



11. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_1 is C_1-C_6 alkyl.

12. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_1 is C_1-C_6 (monohalo or polyhalo)alkyl.

13. A compound of claim 12 wherein C_1-C_6 (monohalo or polyhalo)alkyl is C_1-C_6 monohaloalkyl.

14. A compound of claim 13 wherein C_1-C_6 monohaloalkyl is C_1-C_6 monochloroalkyl.

15. A compound of claim 14 wherein C_1-C_6 monochloroalkyl is chloromethyl.

16. A compound of claim 11 wherein R_2 is C_1-C_6 alkyl or C_1-C_6 monohaloalkyl.

17. A compound of claim 12 wherein R_2 is C_1-C_6 alkyl.

18. A compound of claim 13 wherein R_2 is C_1-C_6 alkyl.

19. A compound of claim 14 wherein R_2 is C_1-C_6 alkyl.

20. A compound of claim 15 wherein R_2 is C_1-C_6 alkyl.

21. A compound of claim 11 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

22. A compound of claim 12 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

23. A compound of claim 13 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

24. A compound of claim 14 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

25. A compound of claim 15 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)alkyl.

26. A compound of claim 1, said compound having the structural formula (I) wherein X is —O—.

27. A compound of claim 12 wherein X is —O—.

28. A compound of claim 13 wherein X is —O—.

29. A compound of claim 14 wherein X is —O—.

30. A compound of claim 17 wherein R_4 and R_5 are hydrogen.

31. A compound of claim 18 wherein R_4 and R_5 are hydrogen.

32. A compound of claim 19 wherein R_4 and R_5 are hydrogen.

33. A compound of claim 20 wherein R_4 and R_5 are hydrogen.

34. A compound of claim 17 wherein at least one of R_4 and R_5 is fluoro.

35. A compound of claim 18 wherein at least one of R_4 and R_5 is fluoro.

36. A compound of claim 19 wherein at least one of R_4 and R_5 is fluoro.

37. A compound of claim 20 wherein at least one of R_4 and R_5 is fluoro.

38. A compound of claim 17 wherein R_4 is fluoro and R_5 is hydrogen.

39. A compound of claim 18 wherein R_4 is fluoro and R_5 is hydrogen.

40. A compound of claim 19 wherein R_4 is fluoro and R_5 is hydrogen.

41. A compound of claim 20 wherein R_4 is fluoro and R_5 is hydrogen.

42. A compound of claim 35 wherein R_3 is α-methyl or β-methyl.

43. A compound of claim 37 wherein R_3 is α-methyl or β-methyl.

44. A compound of claim 39 wherein R_3 is α-methyl or β-methyl.

45. A compound of claim 41 wherein R_3 is α-methyl or β-methyl.

46. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_1 is $—CH_2COOR_6$, $—CH_2—Y—(C_1$-C_6 alkyl) or

$$-CH_2-\overset{O}{\overset{\|}{O}}CR_6'.$$

47. A compound of claim 1, said compound having the structural formula (I) wherein R_1 is $-CH_2CONR_7R_8$.

48. A compound of claim 47 wherein at least one of R_7 and R_8 is hydrogen or C_1–C_6 alkyl.

49. A compound of claim 47 wherein R_7 and R_8 are combined so that $-NR_7R_8$ represents the residue of a saturated monocyclic secondary amine containing 5 to 7 carbon atoms.

50. A compound of claim 49 wherein $-NR_7R_8$ represents morpholino, 1-pyrrolidinyl, 4-benzyl-1-piperazinyl, perhydro-1,2,4-oxathiazin-4-yl, 1- or 4-piperazinyl, 4-methyl-1-piperazinyl, piperidino, hexamethyleneimino, 4-phenylpiperidino, 2-methyl-1-pyrazolidinyl, 1- or 2-pyrazolidinyl, 3-methyl-1-imidazolidinyl, 1- or 3-imidazolidinyl, 4-benzylpiperidino or 4-phenyl-1-piperazinyl.

51. A compound of claim 1, said compound having the structural formula (I) wherein R_1 is

$$-\underset{\underset{R_9}{|}}{CH}-Y\text{-(lower alkyl)}$$

wherein R_9 is hydrogen or methyl, or wherein R_9 and the lower alkyl group adjacent to Y are combined so that R_1 is

$$-\underset{\underset{\text{alkylene}}{|}}{CH}-\underset{|}{Y}$$

wherein Y is —S—, —SO—, —SO_2— or —O— and the alkylene group contains 3 to 10 carbon atoms, of which at least 3 and no more than 6 are ring atoms.

52. A compound of claim 1 or 2, said compound having the structural formula (III) wherein Z is β-hydroxymethylene and R_2 is C_1–C_6 alkyl.

53. A compound of claim 1 or 2, said compound having the structural formula (IV) wherein Z is β-hydroxymethylene and R_2 is C_1–C_6 alkyl.

54. A compound of claim 1 or 2, said compound having the structural formula (VII) wherein Z is β-hydroxymethylene and R_1 is C_1–C_6 alkyl or C_1–C_6 monohaloalkyl.

55. A compound of claim 1 or 2, said compound having the structural formula (VIII) wherein Z is β-hydroxymethylene and R_2 is C_1–C_6 alkyl.

56. A compound of claim 1 or 2, said compound having the structural formula (IX) wherein R_1 is C_1–C_6 (monohalo or polyhalo) alkyl.

57. A compound of claim 56 wherein C_1–C_6 (monohalo or polyhalo)alkyl is C_1–C_6 monohaloalkyl.

58. A compound of claim 57 wherein R_2 is C_1–C_6 alkyl.

59. A compound of claim 1 or 2, said compound having the structural formula (IX) wherein R_1 is C_1–C_6 alkyl or C_1–C_6 monohaloalkyl, R_2 is C_1–C_6alkyl or C_1–C_6 monohaloalkyl and X is —O—.

60. A compound of claim 2, said compound having the structural formula (IX) wherein R_1 is C_1–C_6 alkyl, $-CH_2COOR_6$, $-CH_2-Y-(C_1$–C_6 alkyl) or

$$-CH_2-\overset{O}{\overset{\|}{O}}CR_6'.$$

61. The compound of claim 2 which is chloromethyl 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

62. The compound of claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

63. The compound of claim 2 which is chloromethyl 17β-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

64. The compound of claim 2 which is chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

65. The compound of claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate.

66. The compound of claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate.

67. The compound of claim 2 which is 1-chloroethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

68. The compound of claim 2 which is 1-chloroethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate.

69. The compound of claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate.

70. The compound of claim 2 which is chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate.

71. The compound of claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxyandrosta-1,4-dien-3-one-17β-carboxylate.

72. The compound of claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

73. The compound of claim 2 is chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

74. The compound of claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate.

75. The compound of claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylate.

76. The compound of claim 2 which is chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate.

77. The compound of claim 2 which is fluoromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

78. The compound of claim 2 which is methyl 17α-(2-chloroethoxy)carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

79. The compound of claim 2 which is 17β-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid.

80. The compound of claim 2 which is 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-dien-3-one-17β-carboxylic acid.

81. The compound of claim 2 which is 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylic acid.

82. The compound of claim 2 which is 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylic acid.

83. The compound of claim 2 which is 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid, 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylic acid, or 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylic acid.

84. The compound of claim 2 which is sodium 11β-hydroxy-17α-methoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate, sodium 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, sodium 17α-butoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate, or sodium 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

85. The compound of claim 2 which is chloromethyl 17α-chlorocarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate.

86. The compound of claim 2 which is chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-16α-methylandrosta-1,4-dien-3,11-dione-17β-carboxylate.

87. The compound of claim 2 which is chloromethyl 9α-fluoro-17α-isopropoxycarbonyloxy-16β-methylandrosta-1,4-diene-3,11-dione-17β-carboxylate.

88. A pharmaceutical composition of matter comprising an anti-inflammatory effective amount of a compound of claim 1 or 2 having the structural formula (I), in combination with a non-toxic pharmaceutically acceptable carrier therefor suitable for topical or other local application.

89. A method for alleviating inflammation in or on a warm-blooded animal exhibiting a topical inflammatory response, which comprises topically administering thereto an anti-inflammatory effective amount of a composition of claim 88.

90. A method for alleviating inflammation in or on a warm-blooded animal exhibiting a localized inflammatory response, which comprises locally administering thereto an anit-inflammatory effective amount of composition of claim 88.

91. A compound of claim 13 wherein C_1-C_6 monohaloalkyl is C_1-C_6 monofluoroalkyl.

92. A compound of claim 91 wherein C_1-C_6 monofluoroalkyl is fluoromethyl.

93. A compound of claim 91 wherein R_2 is C_1-C_6 alkyl.

94. A compound of claim 92 wherein R_2 is C_1-C_6 alkyl.

95. A compound of claim 91 wherein X is —I—.

96. A compound of claim 95 wherein R_4 and R_5 are hydrogen.

97. A compound of claim 96 wherein R_3 is hydrogen.

98. A compound of claim 95 wherein at least one of R_4 and R_5 is fluoro.

99. A compound of claim 95 wherein R_4 is fluoro and R_5 is hydrogen.

100. A compound of claim 99 wherein R_3 is α-methyl or β-methyl.

101. A compound of claim 2 which is fluoromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate.

102. The compound of claim 2 which is fluoromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate.

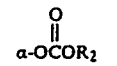
103. The compound of claim 2 which is fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-n-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate.

104. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_3, R_4 and R_5 are hydrogen and the 1,2 linkage is saturated or unsaturated.

105. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_3 is selected from hydrogen or methyl, R_4 is fluoro and R_5 is hydrogen and the 1,2 linkage is saturated or unsaturated.

106. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_3 is hydrogen or methyl, R_4 is hydrogen or fluoro and R_5 is fluoro or methyl and the 1,2 linkage is unsaturated.

107. A compound of claim 1 or 2, said compound having the structural formula (I) wherein R_3 is

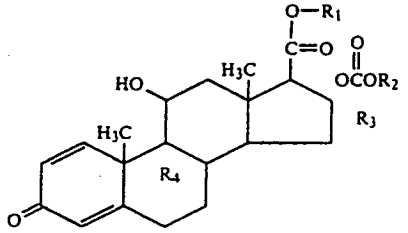


and wherein R_4 is fluoro and R_5 is hydrogen and the 1,2 linkage is unsaturated.

108. A compound of claim 59 wherein R_3 is hdyrogen or methyl, R_4 is hydrogen and R_5 is hydrogen or chloro and the 1,2 linkage is saturated or unsaturated.

109. The compound of claim 45 wherein R_3 is α-methyl and the 1,2 linkage is unsaturated.

110. A compound of the formula

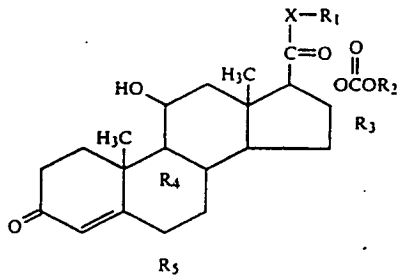


wherein R_1 is C_1-C_6 (monohalo)alkyl, R_2 is C_1-C_6 alkyl, R_3 is hydrogen, α-methyl or β-methyl and R_4 is hydrogen or fluoro.

111. A compound of claim 110 wherein R_1 is chloromethyl.

112. A compound of claim 110 wherein R_3 is α-methyl and R_4 is fluoro.

113. A compound of the formula



(I)

wherein:

R_1 is $—CH_2COOR_6$ wherein R_6 is C_1-C_6 alkyl; $—CH_2—Y—(C_1$-C_6 alkyl) wherein Y is —S—, —SO—, $—SO_2—$ or —O—; or

$$-CH_2OCR_6'$$

wherein R_6' is C_1–C_6 alkyl or phenyl;

R_2 is C_1–C_6 alkyl, C_3–C_8 cycloalkyl, phenyl, benzyl or C_1–C_6 (monohalo or polyhalo)alkyl;

R_3 is hydrogen, α-hydroxy, α-methyl, β-methyl or

$$\alpha\text{-}OCOR_2 .$$

wherein R_2 is as defined above;

R_4 is hydrogen or fluoro;

R_5 is hydrogen or fluoro;

X is —O— or —S—;

and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated.

* * * * *

Patent
Attorney Docket: 003800-006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	)	**ATTENTION:**
	)	**CERTIFICATE OF**
Nicholas S. BODOR	)	**CORRECTION BRANCH**
	)	
Patent No. 4,996,335	)	Serial No.: 06/807,034
	)	
Issued: February 26, 1991	)	Filed: December 9, 1985
	)	
For: SOFT STEROIDS HAVING ANTI-INFLAMMATORY ACTIVITY	)	

REQUEST FOR ISSUANCE OF CERTIFICATE OF CORRECTION

Assistant Commissioner for Patents
Washington, D.C. 20231

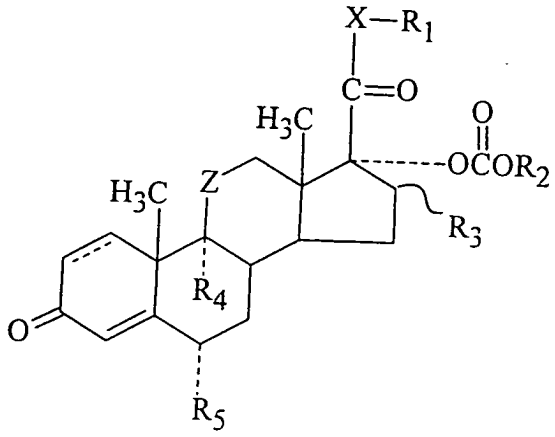
Sir:

Patentee hereby requests that the Commissioner issue a Certificate of Correction directed to the above-identified patent in view of errors that occurred during the printing thereof.

The corrections, which are also set forth on the enclosed duplicate originals of Form PTO-1050, are as follows:

In Column 1, line 9, "Sept. 18" should read --Sept. 15--.

In Column 2, lines 45-57, delete the structural formula (I), and insert in its stead:

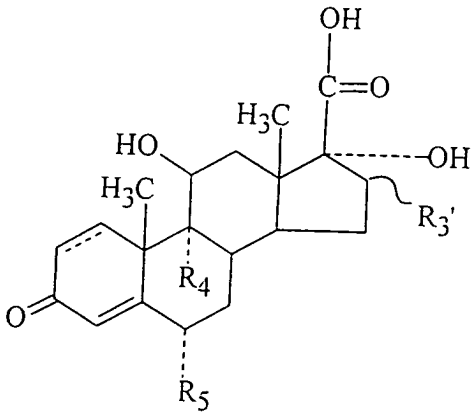


(I)

In Column 5, line 25, "timethylene" should read --trimethylene--.

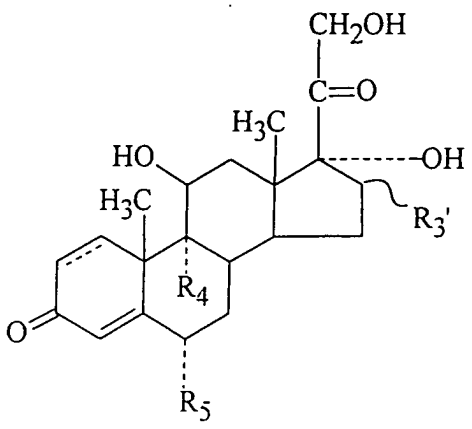
In Column 5, lines 28 and 29, after "dialkylcarbamoyl", insert --groupings are of the type--.

In Column 10, lines 1-13, delete the structural formula (II) and insert in its stead:

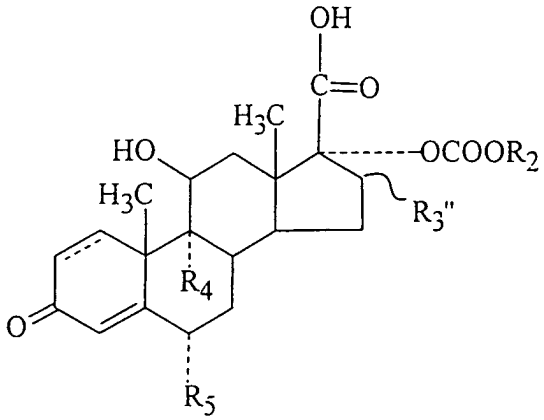


(II)

In Column 10, lines 20-30, delete the structural formula and insert in its stead:

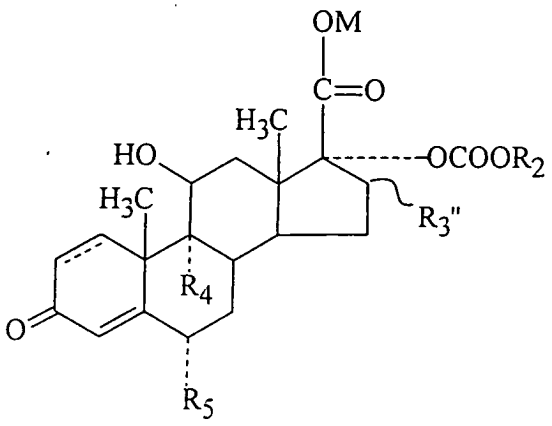


In Column 10, lines 50-60, delete the structural formula (III) and insert in its stead:



(III)

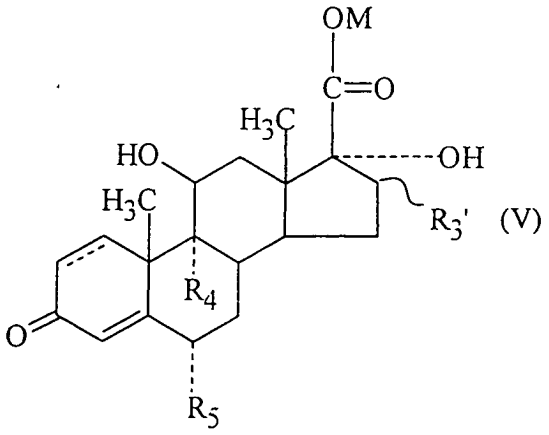
In Column 11, lines 15-25, delete the structural formula (IV) and insert in its stead:



(IV)

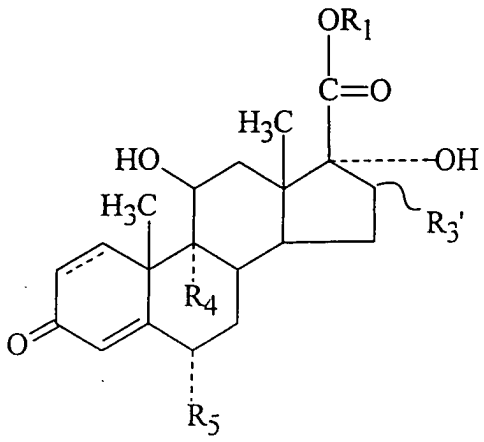
In Column 12, line 8, "wtih" should read --with--.

In Column 13, lines 1-12, delete structural formula (V) and insert in its stead:



(V)

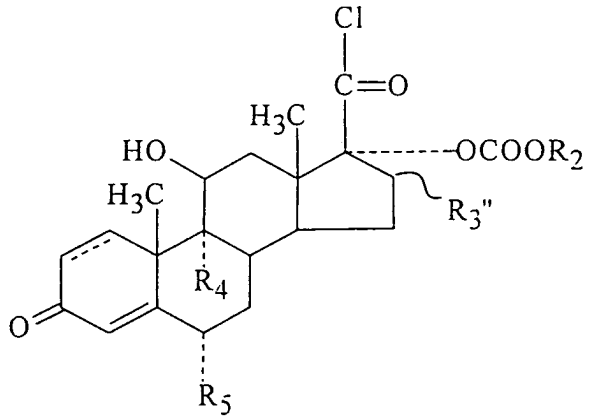
In Column 13, lines 18-29, delete the structural formula (VI) and insert in its stead:



(VI)

In Column 13, line 50, after "formula (I) wherein R_1 is", insert --a sulfinyl- or sulfonyl-containing group [e.g., when R_1 is--.

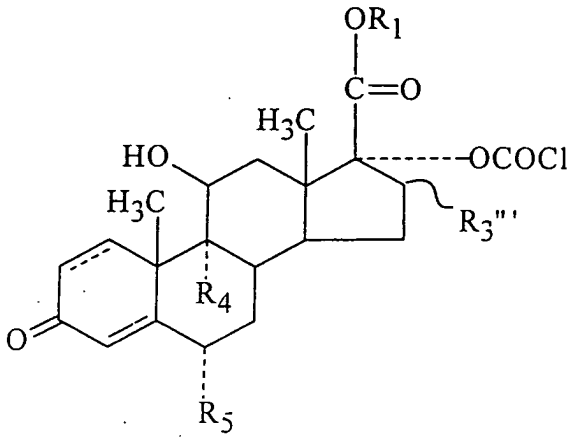
In Column 14, lines 5-17, delete the structural formula (VIII) and insert in its stead:



(VIII)

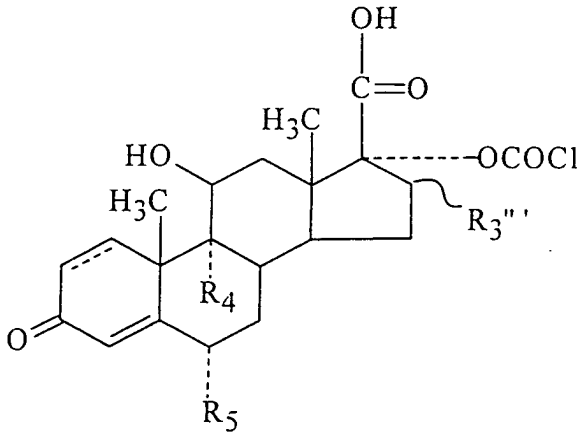
In Column 14, line 42, "phuosgene" should read --phosgene--.

In Column 14, lines 45-57, delete the structural formula (VII) and insert in its stead:



(VII)

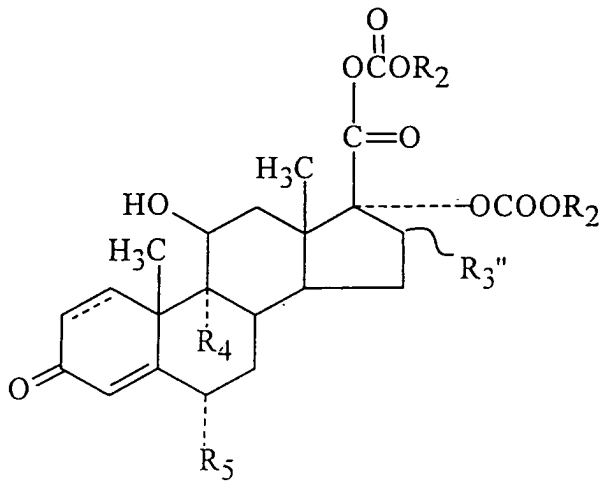
In Column 15, lines 23-34, delete the structural formula (X) and insert in its stead:



(X)

In Column 16, line 40, "aceytonitrile" should read --acetonitrile--.

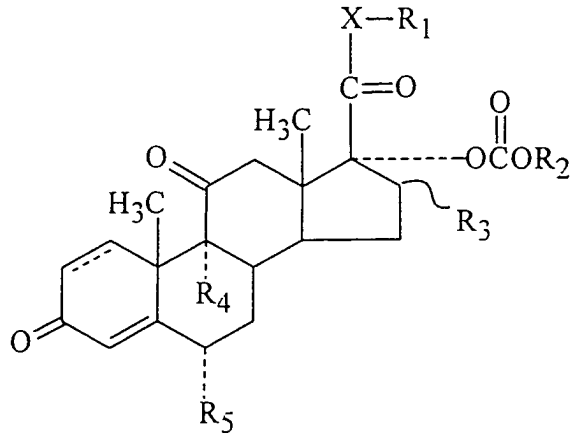
In Column 16, lines 55-68, delete the structural formula (XI) and insert in its stead:



(XI)

In Column 17, line 25, "suchy" should read --such--.

In Column 17, lines 36-46, delete the structural formula (IX) and insert in its stead:



(IX)

In Column 18, line 20, "and" should read --an--.

In Column 18, line 60, "As" should read --An--.

In Column 20, line 3, "MeKenzie" should read --McKenzie--.

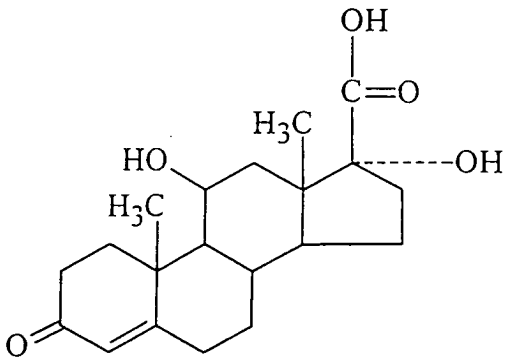
In Column 26, line 63, "asigned" should read --assigned--.

In Column 33, line 24, after "tioned", the period (".") should be a colon (--:--).

In Column 33, line 32, "propylactic" should read --prophylactic--.

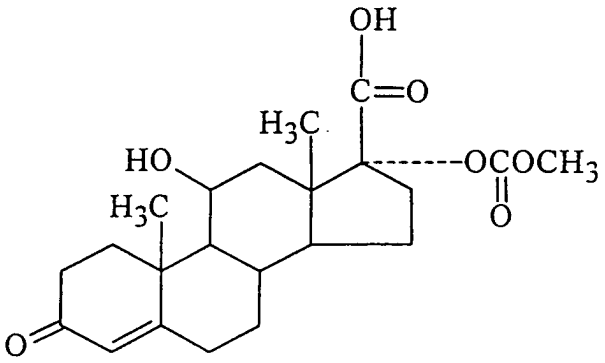
In Column 34, line 39, "17α/e-" should read --17α-e- --.

In Column 35, lines 47-58, delete the structural formula and insert in its stead:

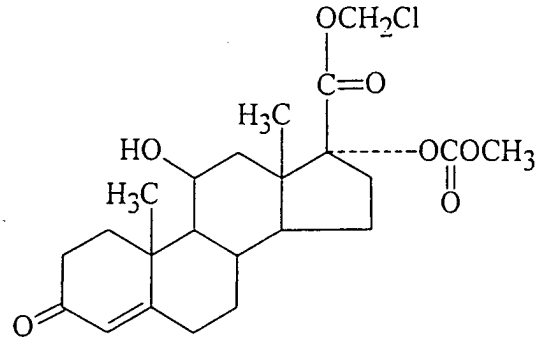


In Column 35, lines 67-68, "filtration" should read --filtrate--.

In Column 36, lines 12-23, delete the structural formula and insert in its stead:



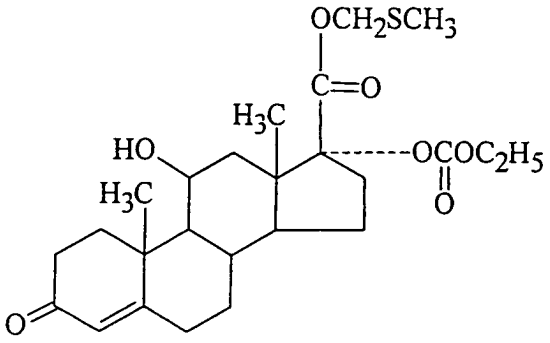
In Column 37, lines 15-25, delete the structural formula and insert in its stead:



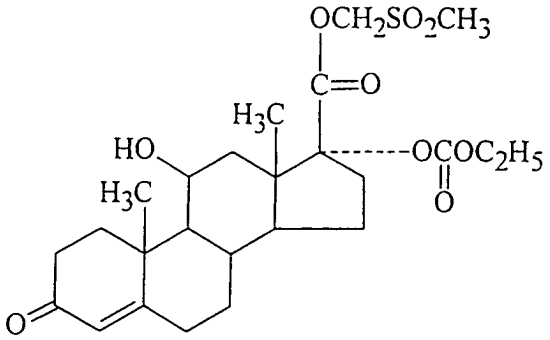
In Column 37, line 53, after "nmr($CDCl_3$)" and before "δ5.60", insert --δ5.80,--.

In Column 38, line 24, "mmol6)" should read --mmol)--.

In Column 38, lines 51-61, delete the structural formula and insert in its stead:



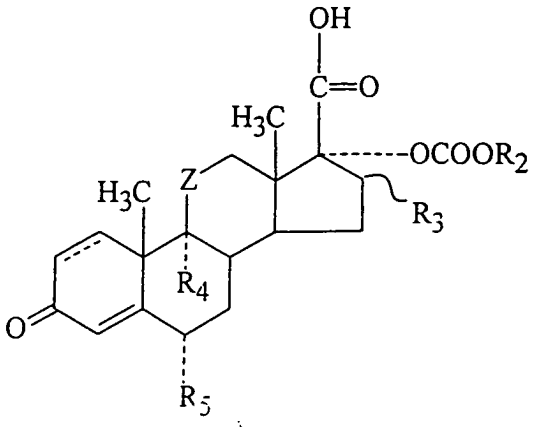
In Column 39, lines 6-16, delete the structural formula and insert in its stead:



In Column 39, line 22, "17β-ethoxycarbonyloxy" should read --17α-ethoxycarbonyloxy--.

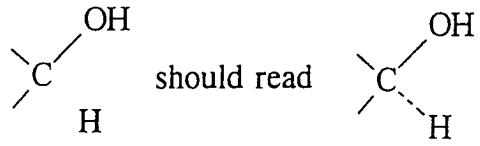
In Column 40, line 18, "11α,17β-dihydroxy" should read --11β,17α-dihydroxy--.

In Column 40, lines 35-46, delete the structural formula and insert in its stead:



In Column 40, line 48, delete "Compounds".

In Columns 40 and 41, in the table in Example 6A, for each of Compound Nos. 6A-1 through 6A-15, under column "Z", at each occurrence,

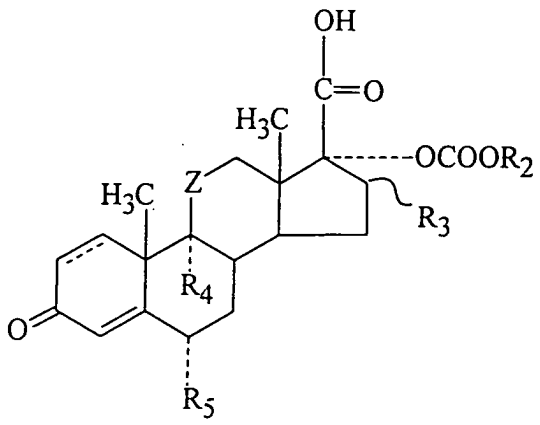


In Column 41, line 60, at the bottom of the table, before "6a-1 to 6A-15 above", insert --Compounds--.

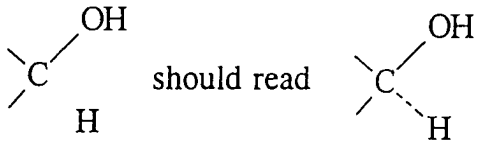
In Column 41, line 62, "17α-benzyloxo" should read --17α-benzyloxy--.

In Column 43, line 13, "aicd" should read --acid--.

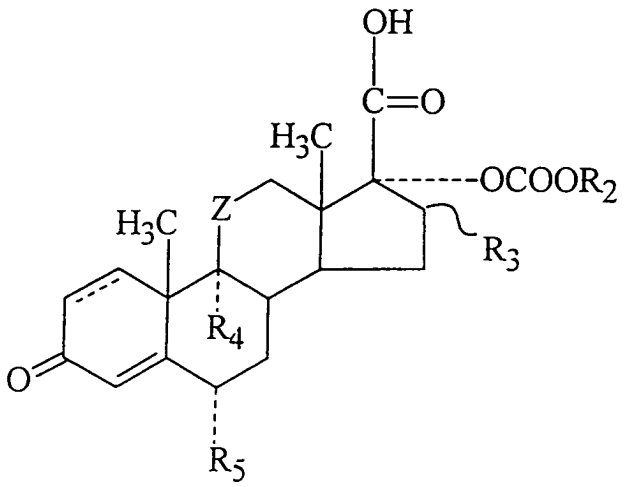
In Column 44, lines 10-21, delete the structural formula and insert in its stead:



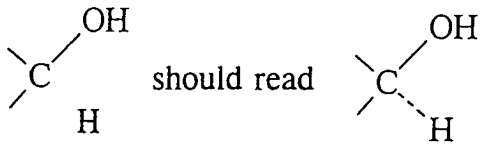
In Columns 44, 45-46 and 47-48, in the table in Example 6B, for each of Compound Nos. 6B-3, 6B-4, 6B-5, 6B-7, 6B-8, 6B-9, 6B-11, 6B-12, 6B-13, and 6B-15 through 6B-25, under column "Z", at each occurrence,



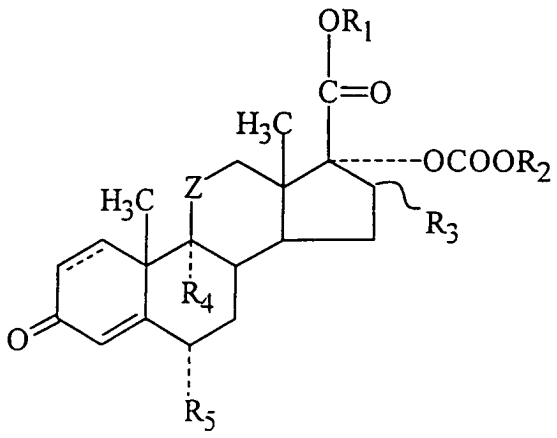
In Column 48, lines 15-26, delete the structural formula (VI) and insert in its stead:



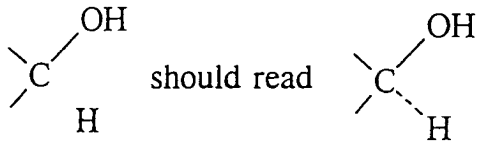
In Columns 48 and 49-50, in the table in Example 6C, for each of Compound Nos. 6C-1 through 6C-11, under column "Z", at each occurrence,



In Column 50, lines 33-45, delete the structural formula and insert in its stead:



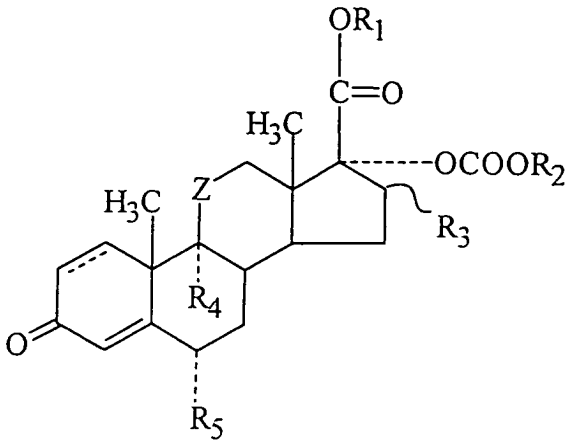
In Columns 50 through 56, in the table in Example 7A, for each of Compound Nos. 7A-1 through 7A-18 and 7A-21 through 7A-30, under column "Z", at each occurrence,



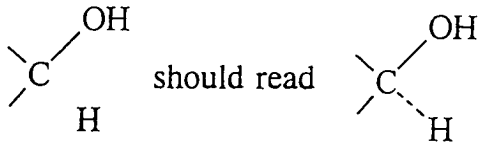
In Column 55, line 20, "17β-ethoxycarbonyloxy" should read --17α-ethoxycarbonyloxy--.

In Column 56, line 14, "methylandrost" should read --methylandrosta--.

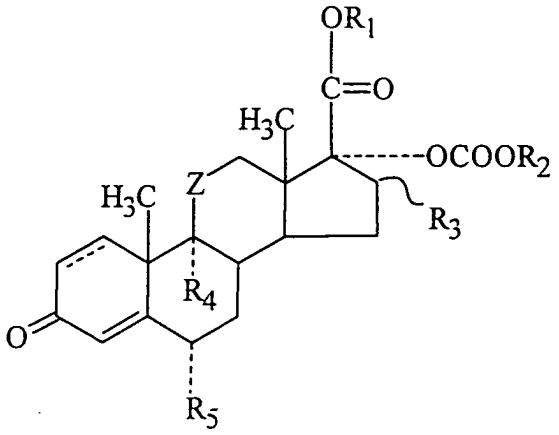
In Column 56, lines 46-56, delete the structural formula and insert in its stead:



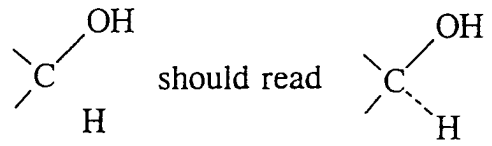
In Columns 56 through 66, in the table in Example 7B, for each of Compound Nos. 7B-1 through 7B-7, 7B-14 through 7B-18, 7B-22 through 7B-29, 7B-33 through 7B-40, and 7B-44 through 7B-64, under column "Z", at each occurrence,



In Column 66, lines 40-50, delete the structural formula and insert in its stead:

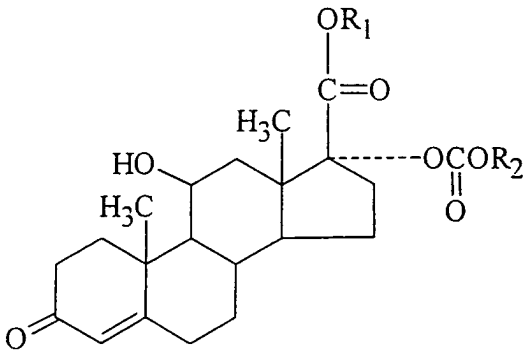


In Columns 66 through 68, in the table in Example 7C, for each of Compound Nos. 7C-1 through 7C-13, under column "Z", at each occurrence,



In Column 69, line 39, "11α," should read --11β,--.

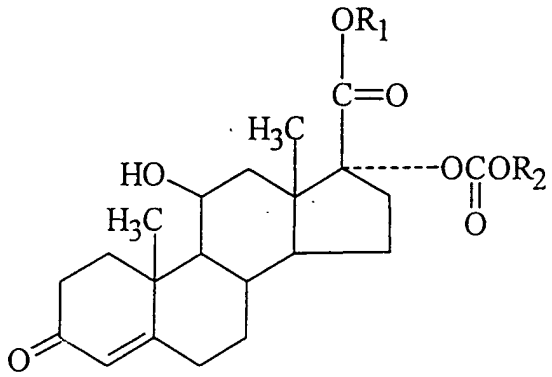
In Column 69, lines 52-62, delete the structural formula and insert in its stead:



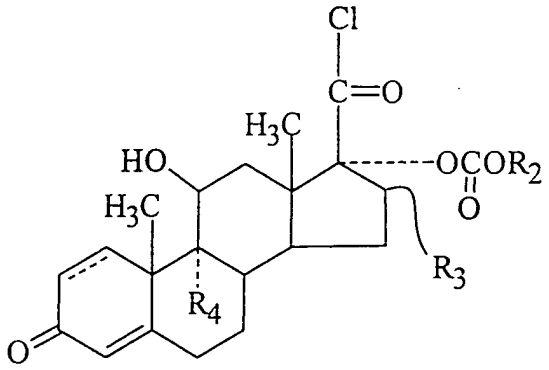
In Column 70, lines 3-13, delete the structural formula.

In Column 70, line 31, "thylfulfonylmethyl" should read --thylsulfonylmethyl--.

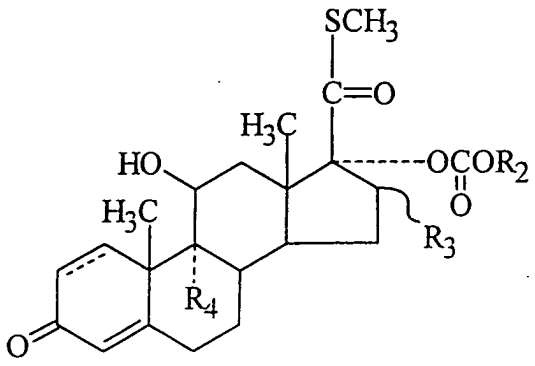
In Column 70, lines 37-46, delete the structural formula and insert in its stead:



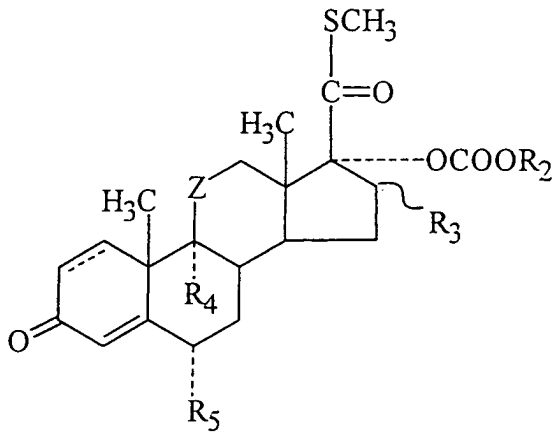
In Column 71, lines 2-11, delete the structural formula and insert in its stead:



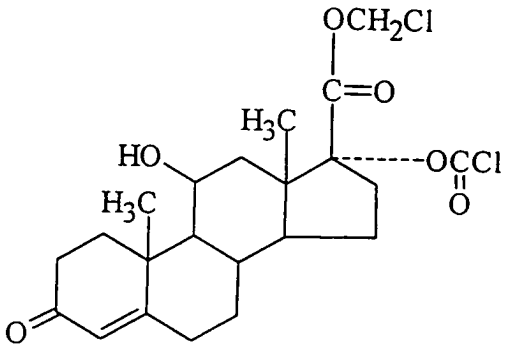
In Column 71, lines 22-31, delete the structural formula and insert in its stead:



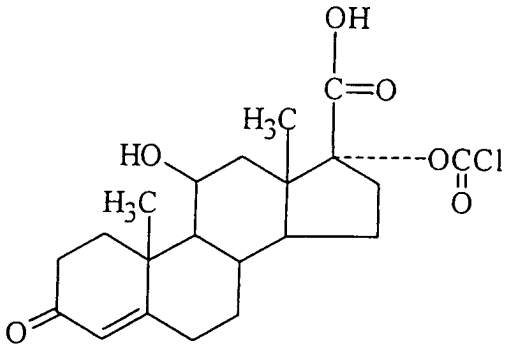
In Column 71, lines 44-54, delete the structural formula and insert in its stead:



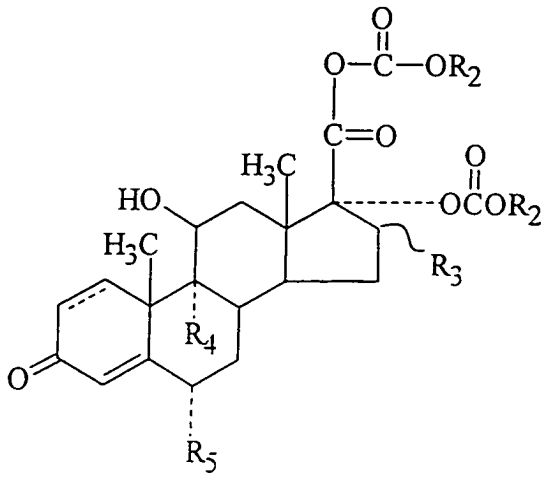
In Column 72, lines 5-13, delete the structural formula and insert in its stead:



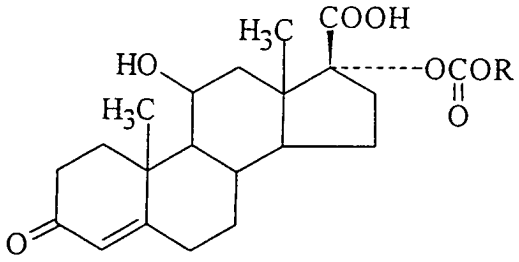
In Column 72, lines 51-60, delete the structural formula and insert in its stead:



In Column 74, lines 2-14, delete the structural formula and insert in its stead:

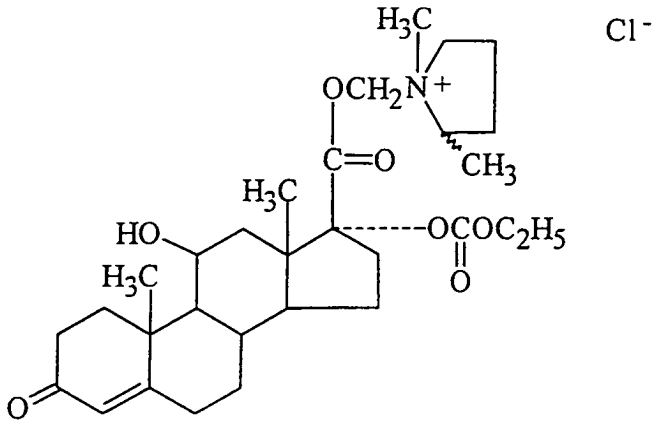


In Column 74, lines 47-55, delete the structural formula and insert in its stead:

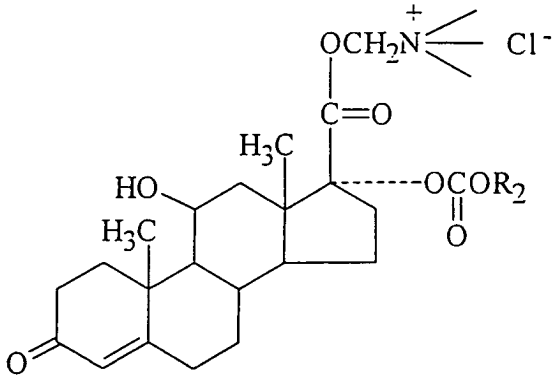


In Column 76, line 6, "dikmethylpyrrolidine" should read --dimethylpyrrolidine--.

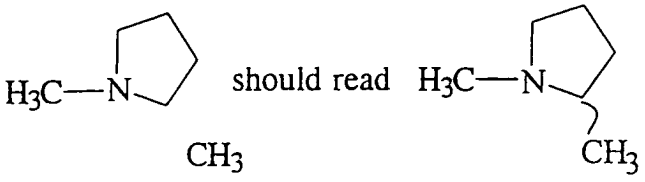
In Column 76, lines 17-30, delete the structural formula and insert in its stead:



In Column 76, lines 37-48, delete the structural formula and insert in its stead:

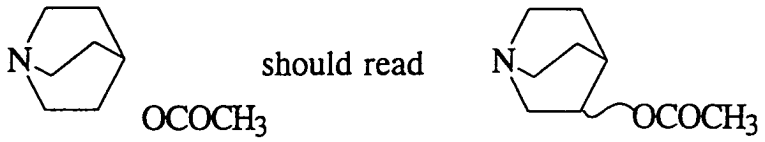


In Column 76, lines 52-55,



In Column 77, lines 3-12, delete the structural formula.

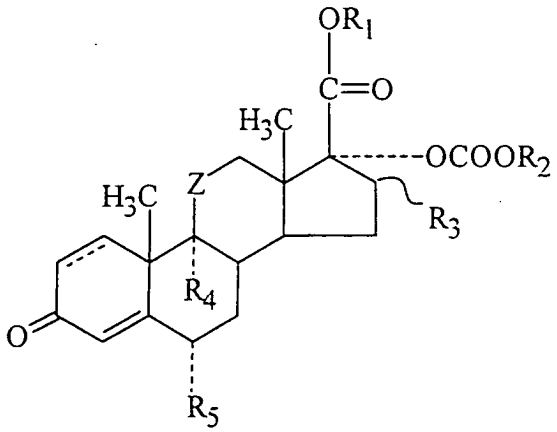
In Column 77, lines 17-20,



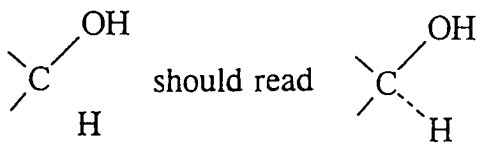
In Column 77, lines 57-58, "Benalkonium" should read --Benzalkonium--.

In Column 78, line 38, "Eye Drops" should be underlined.

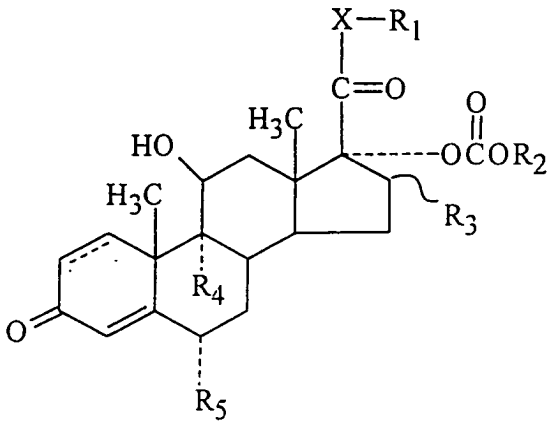
In Column 79, lines 14-25, delete the structural formula and insert in its stead:



In Columns 79-80, lines 24-38, in the table in Example 29, for each of Compound Nos. 29-1 and 29-2, under column "Z", at each occurrence,

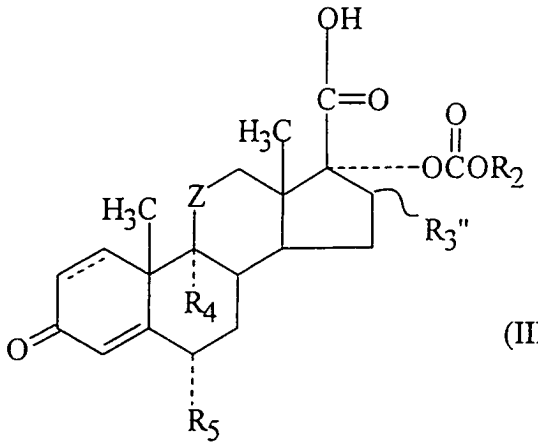


In Column 80, lines 2-12, part (a) of Claim 1, delete the structural formula (I) and insert in its stead:



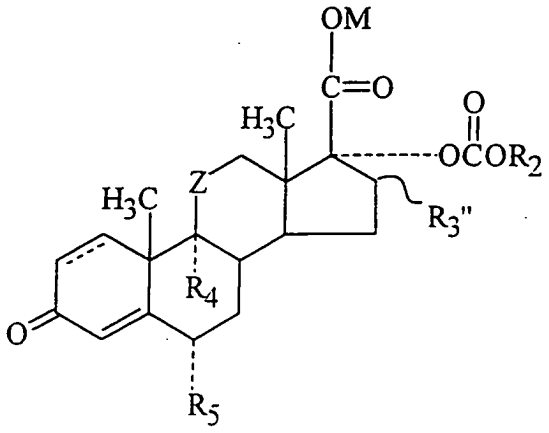
(I)

In Column 81, lines 55-65, part (c) of Claim 1, delete the structural formula and insert in its stead:



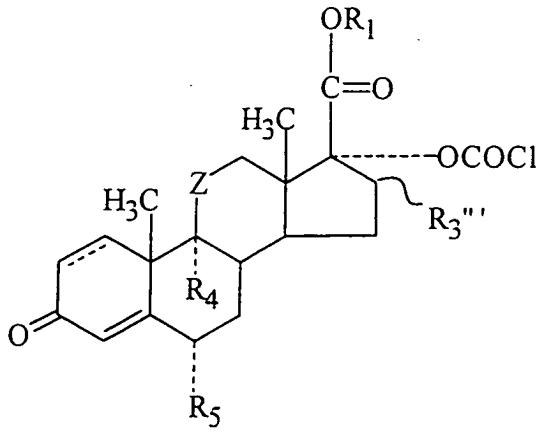
(III)

In Column 82, lines 15-24, part (d) of Claim 1, delete the structural formula (IV) and insert in its stead:



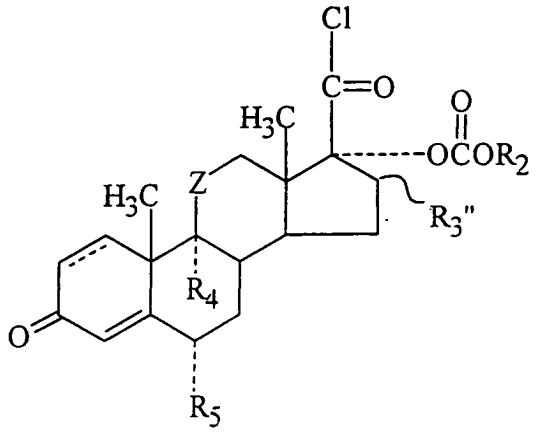
(IV)

In Column 82, lines 34-44, part (e) of Claim 1, delete the structural formula (VII) and insert in its stead:



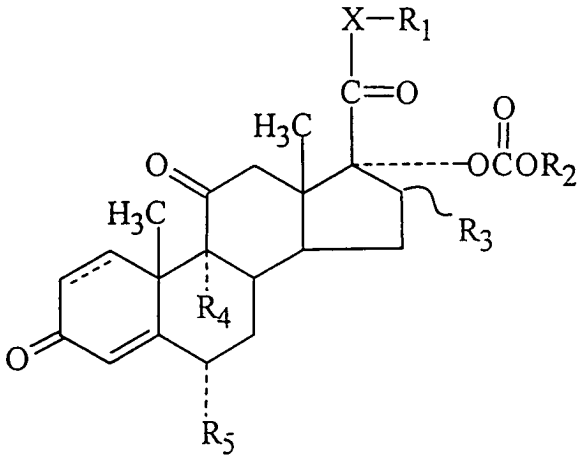
(VII)

In Column 82, lines 53-64, part (f) of Claim 1, delete the structural formula (VIII) and insert in its stead:



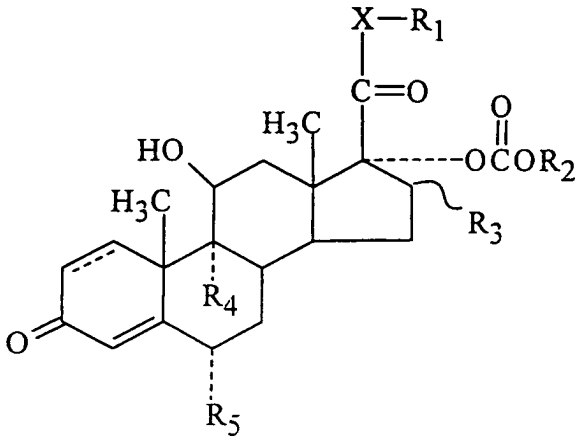
(VIII)

In Column 83, lines 2-12, part (g) of Claim 1, delete the structural formula (IX) and insert in its stead:



(IX)

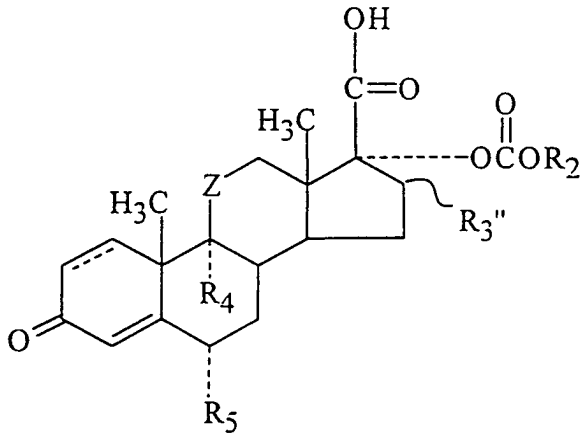
In Column 83, lines 20-31, part (a) of Claim 2, delete the structural formula (I) and insert in its stead:



(I)

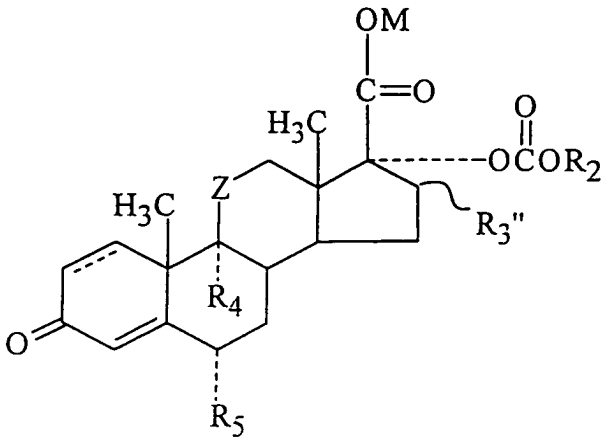
In Column 83, line 49, part (a) of Claim 2, in the definition of R_3, "β-methyl, β-methyl" should read --α-methyl, β-methyl--.

In Column 84, lines 2-13, part (c) of Claim 2, delete the structural formula (III) and insert in its stead:



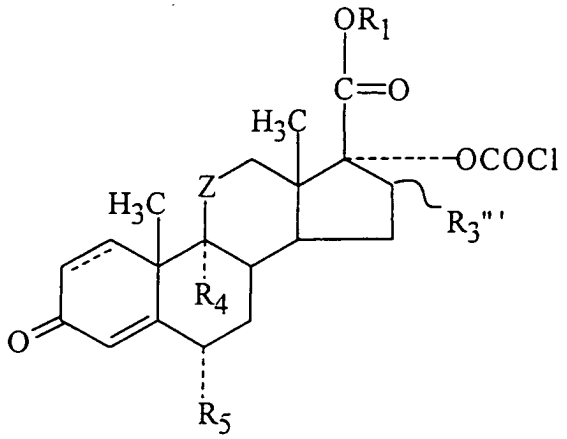
(III)

In Column 84, lines 31-43, part (d) of Claim 2, delete the structural formula (IV) and insert in its stead:



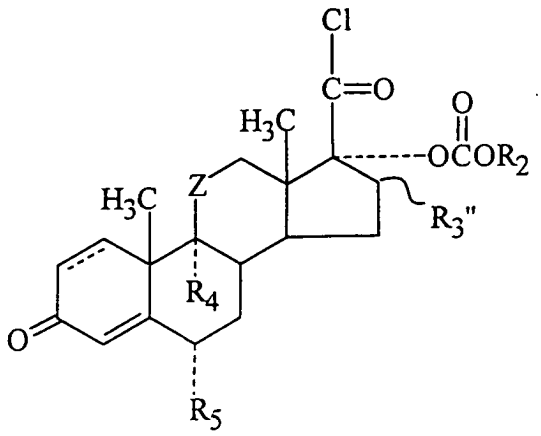
(IV)

In Column 84, lines 51-62, part (e) of Claim 2, delete the structural formula (VII) and insert in its stead:



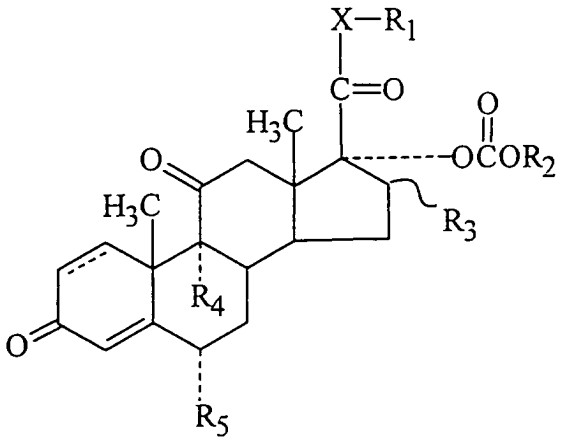
(VII)

In Column 85, lines 2-12, part (f) of Claim 2, delete the structural formula (VIII) and insert in its stead:



(VIII)

In Column 85, lines 18-28, part (g) of Claim 2, delete the structural formula (IX) and insert in its stead:



(IX)

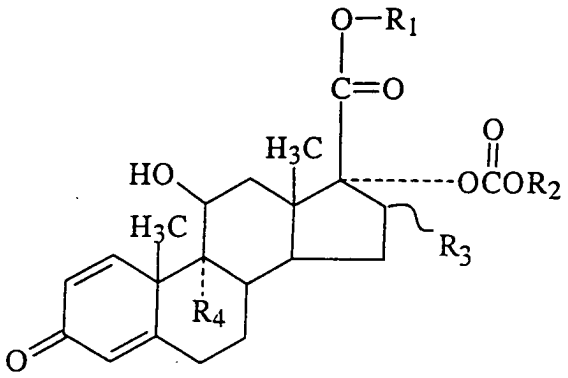
In Column 87, line 16, Claim 50, "sentss" should read --sents--.

In Column 88, line 42, Claim 73, after "claim 2" and before "is", insert --which--.

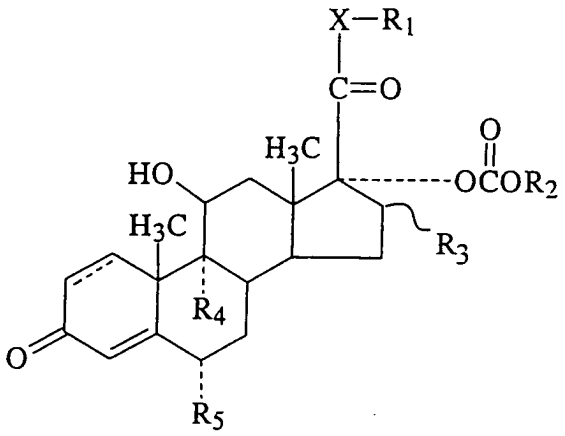
In Column 89, line 24, Claim 86, "dien" should read --diene--.

In Column 89, line 53, Claim 95, delete "-I-" and insert -- -O- --.

In Column 90, lines 33-42, Claim 110, delete the structural formula and insert in its stead:



In Column 90, lines 52-63, Claim 113, delete the structural formula (I) and insert in its stead:



(I)

The above information was correct in the application as filed on December 9, 1985 and as amended by amendments filed December 9, 1985 and September 9, 1987.

It is hereby requested that, in view of the above, a Certificate of Correction be issued. In addition, since the errors are printing errors and are the mistake of the Patent Office, the Certificate should be issued at no charge to the patentee.

Respectfully submitted,

BURNS, DOANE, SWECKER AND MATHIS, L.L.P.

By _____
Norman H. Stepno
Registration No. 22,716

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: March 23, 1998

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231

APR 02'98

U.S. OFFICIAL MAIL
PENALTY FOR PRIVATE USE $300
PB METER
7250474
020
U.S. POSTAGE

A request for a Certificate of Correction has been received for U.S. Patent 4996335

NORMAN H. STEPNO
BURNS, DOANE, SWECKER & MATHIS L.L.P
P.O.BOX 1404
ALEXANDRIA, VIRGINIA 22313-1404

003800-006

Staple Here Only !

PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE

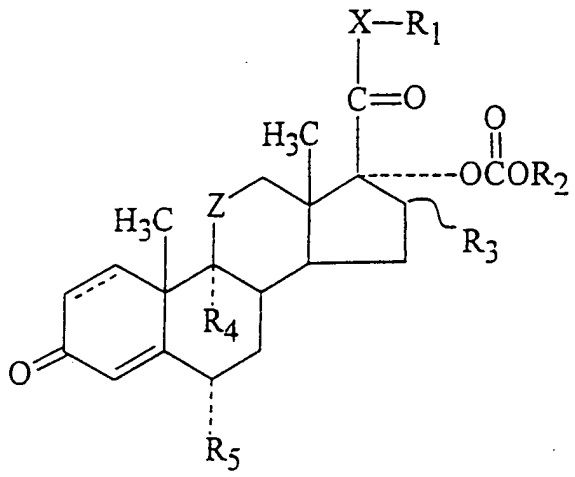
CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 1, line 9, "Sept. 18" should read --Sept. 15--.

In Column 2, lines 45-57, delete the structural formula (I), and insert in its stead:



(I)

In Column 5, line 25, "timethylene" should read --trimethylene--.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

UNITED STATES PATENT AND TRADEMARK OFFICE

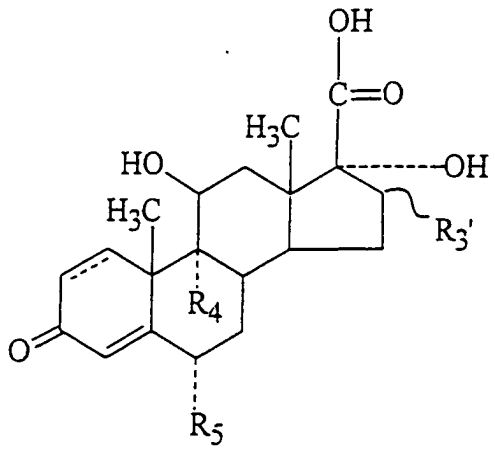
CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 5, lines 28 and 29, after "dialkylcarbamoyl", insert –groupings are of the type–.

In Column 10, lines 1-13, delete the structural formula (II) and insert in its stead:



(II)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

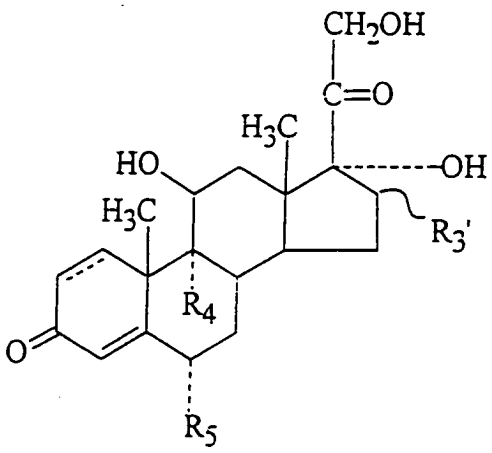
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 10, lines 20-30, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

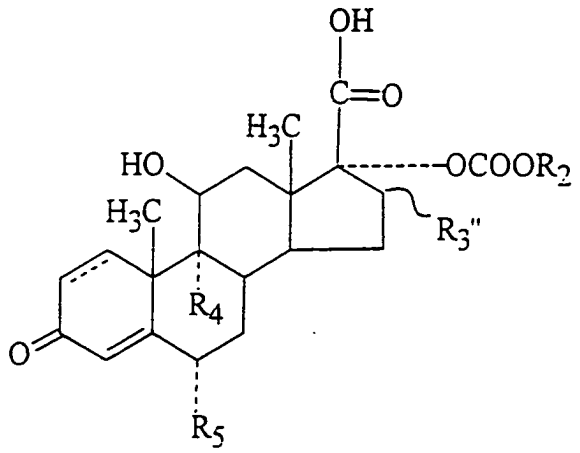
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 10, lines 50-60, delete the structural formula (III) and insert in its stead:



(III)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

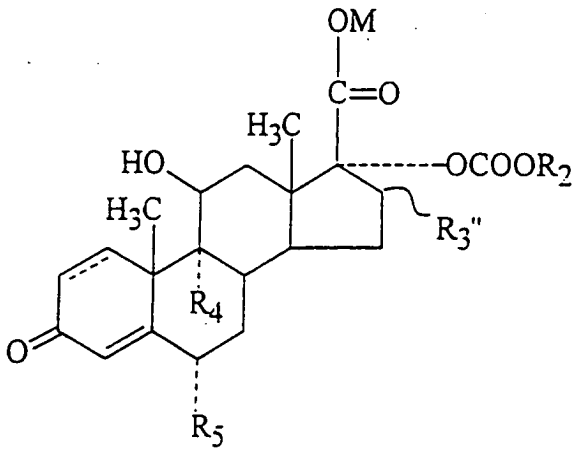
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 11, lines 15-25, delete the structural formula (IV) and insert in its stead:



(IV)

In Column 12, line 8, "wtih" should read –with–.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

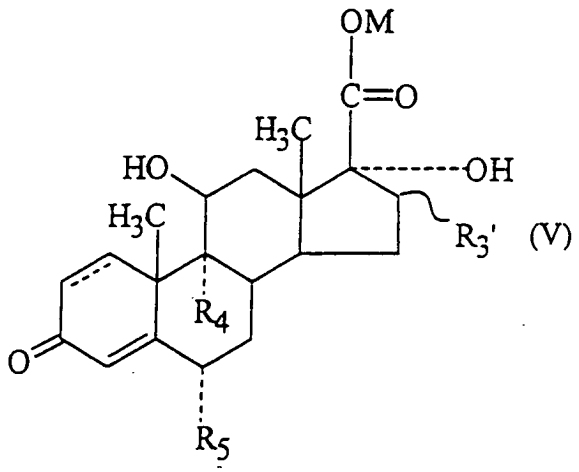
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 13, lines 1-12, delete structural formula (V) and insert in its stead:



MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

FORM PTO 1050 (Rev. 2-93)

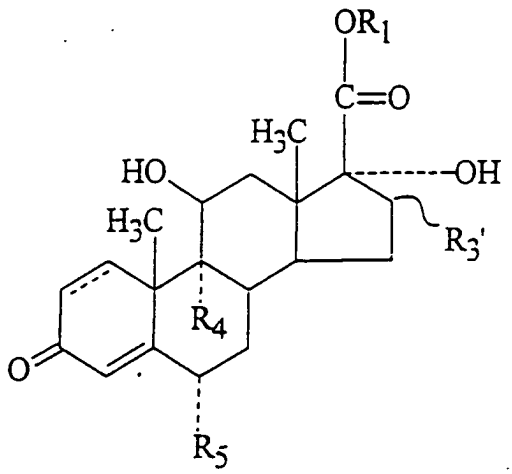
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 13, lines 18-29, delete the structural formula (VI) and insert in its stead:



(VI)

In Column 13, line 50, after "formula (I) wherein R_1 is", insert –a sulfinyl- or sulfonyl-containing group [e.g., when R_1 is–.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

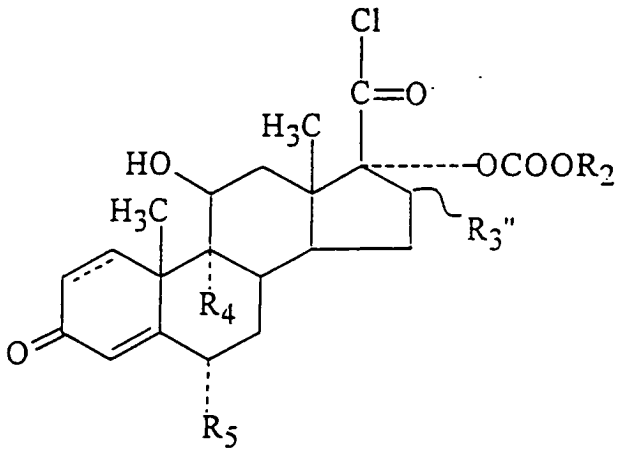
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 14, lines 5-17, delete the structural formula (VIII) and insert in its stead:



(VIII)

In Column 14, line 42, "phuosgene" should read –phosgene–.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

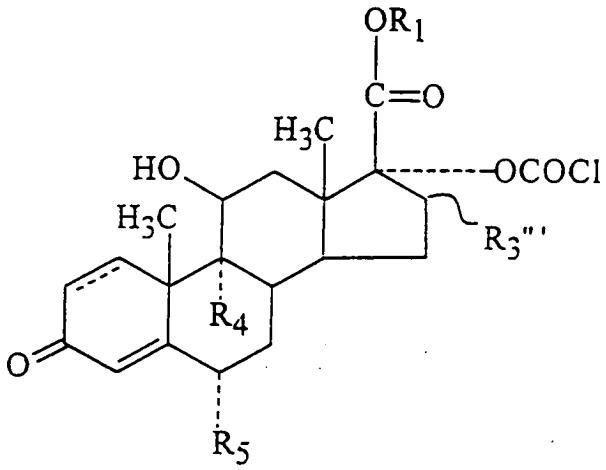
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 14, lines 45-57, delete the structural formula (VII) and insert in its stead:



(VII)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

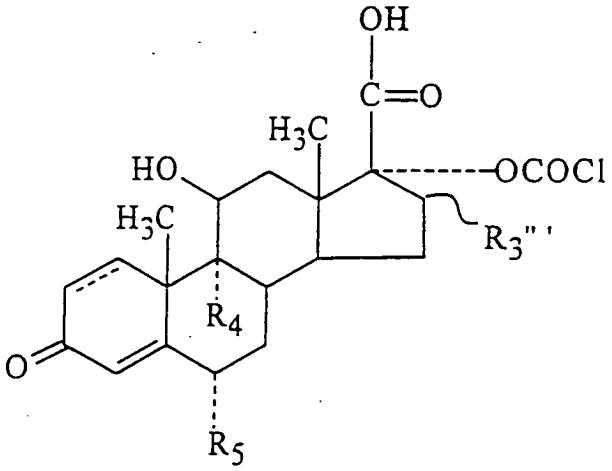
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 15, lines 23-34, delete the structural formula (X) and insert in its stead:



(X)

In Column 16, line 40, "aceytonitrile" should read –acetonitrile–.

MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

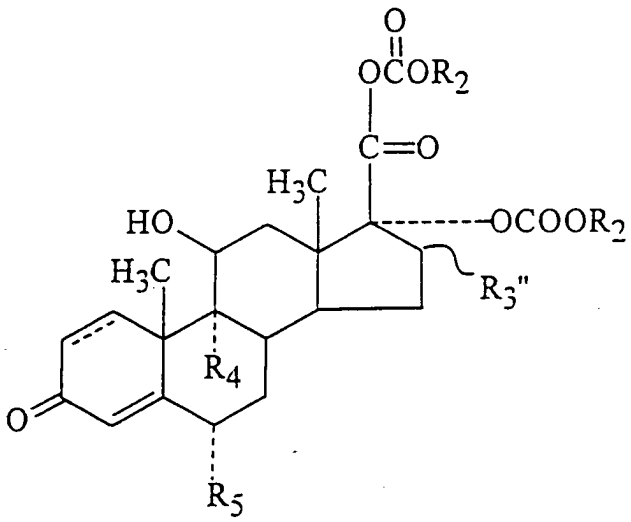
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 16, lines 55-68, delete the structural formula (XI) and insert in its stead:



(XI)

In Column 17, line 25, "suchy" should read --such--.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

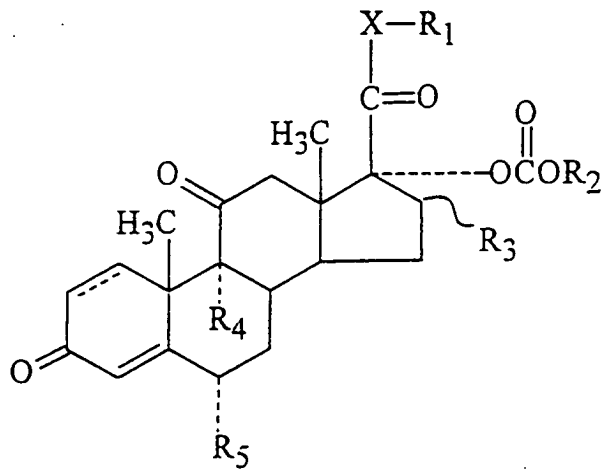
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 17, lines 36-46, delete the structural formula (IX) and insert in its stead:



(IX)

In Column 18, line 20, "and" should read –an–.

MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

No. of add'l copies @ 50¢ per page

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 18, line 60, "As" should read --An--.

In Column 20, line 3, "MeKenzie" should read --McKenzie--.

In Column 26, line 63, "asigned" should read --assigned--.

In Column 33, line 24, after "tioned", the period (".") should be a colon (--:--).

In Column 33, line 32, "propylactic" should read --prophylactic--.

In Column 34, line 39, "17α/e-" should read --17α-e- --.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

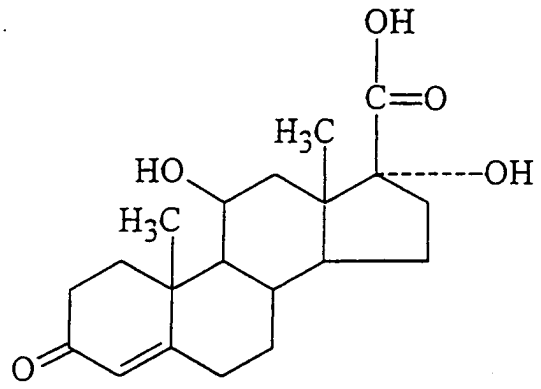
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 35, lines 47-58, delete the structural formula and insert in its stead:



In Column 35, lines 67-68, "filtration" should read --filtrate--.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

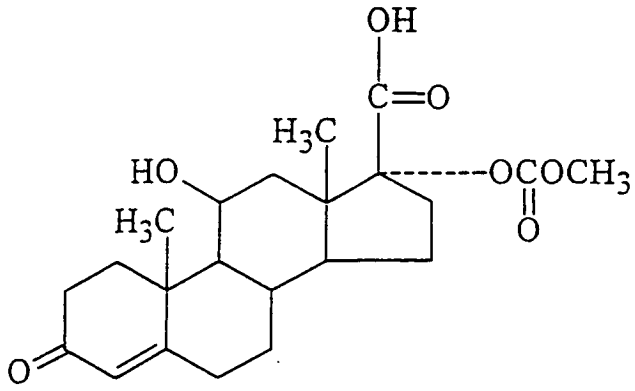
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 36, lines 12-23, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

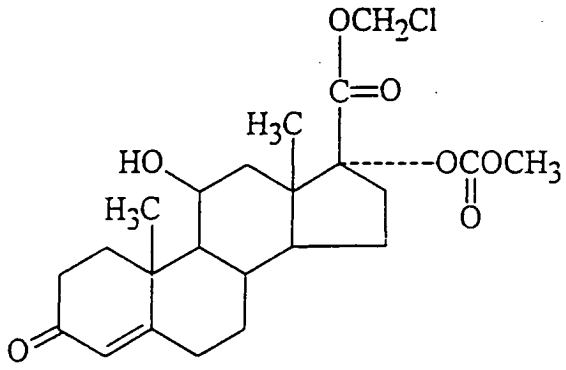
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 37, lines 15-25, delete the structural formula and insert in its stead:



In Column 37, line 53, after "nmr($CDCl_3$)" and before "δ5.60", insert –δ5.80,–.

In Column 38, line 24, "mmol6)" should read –mmol)–.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

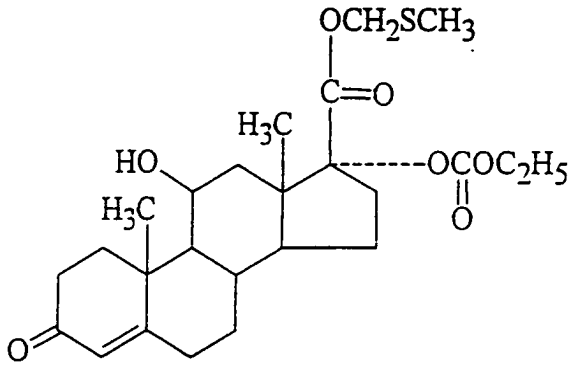
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 38, lines 51-61, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of addt'l copies @ 50¢ per page

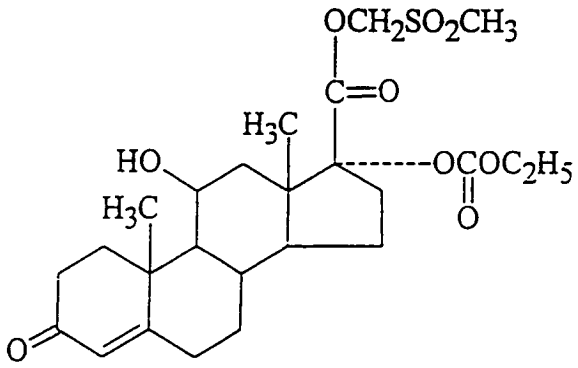
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 39, lines 6-16, delete the structural formula and insert in its stead:



In Column 39, line 22, "17β-ethoxycarbonyloxy" should read --17α-ethoxycarbonyloxy--.

In Column 40, line 18, "11α,17β-dihydroxy" should read --11β,17α-dihydroxy--.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

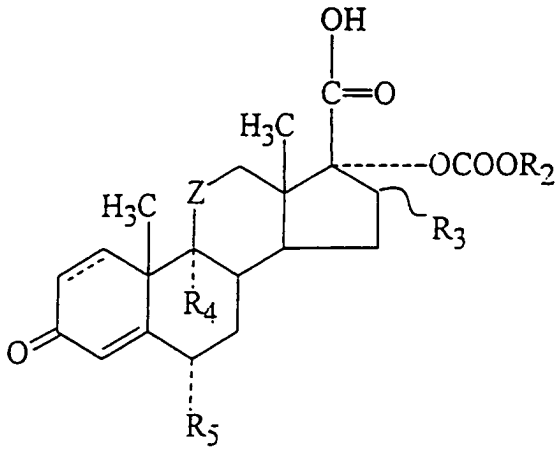
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 40, lines 35-46, delete the structural formula and insert in its stead:



In Column 40, line 48, delete "Compounds".

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

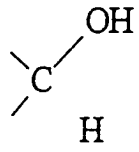
No. of add'l copies @ 50¢ per page

CERTIFICATE OF CORRECTION

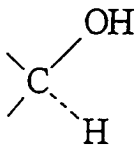
PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Columns 40 and 41, in the table in Example 6A, for each of Compound Nos. 6A-1 through 6A-15, under column "Z", at each occurrence,



should read



In Column 41, line 60, at the bottom of the table, before "6a-1 to 6A-15 above", insert –Compounds–.

In Column 41, line 62, "17α-benzyloxo" should read –17α-benzyloxy–.

In Column 43, line 13, "aicd" should read –acid–.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

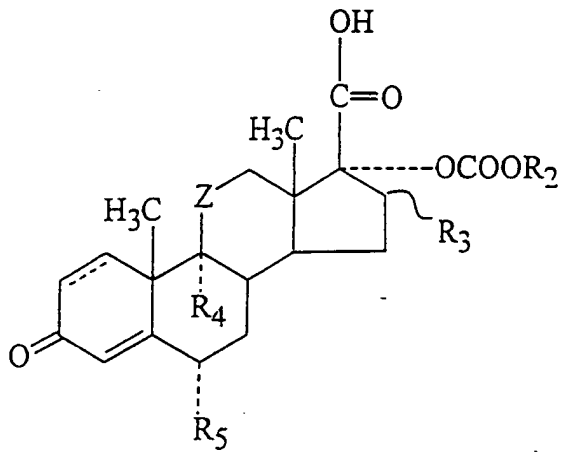
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 44, lines 10-21, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

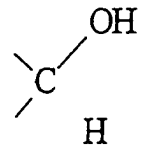
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

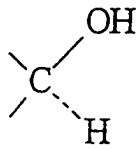
PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Columns 44, 45-46 and 47-48, in the table in Example 6B, for each of Compound Nos. 6B-3, 6B-4, 6B-5, 6B-7, 6B-8, 6B-9, 6B-11, 6B-12, 6B-13, and 6B-15 through 6B-25, under column "Z", at each occurrence,



should read



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of addt'l copies @ 50¢ per page

Staple Here Only !

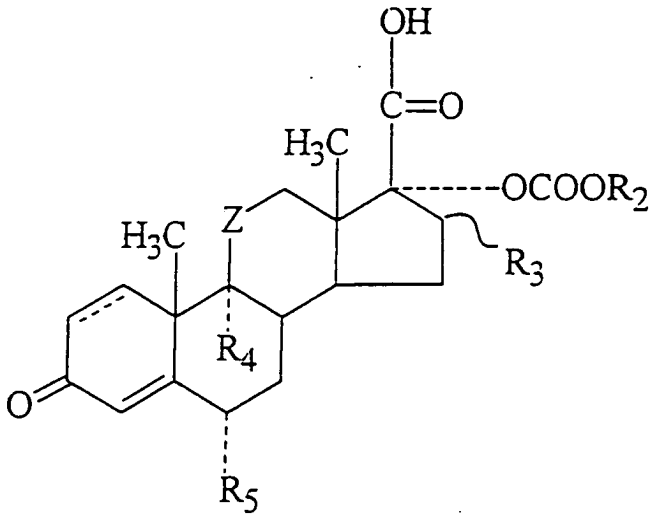
PRINTER'S TRIM LINE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 48, lines 15-26, delete the structural formula (VI) and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of addl copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

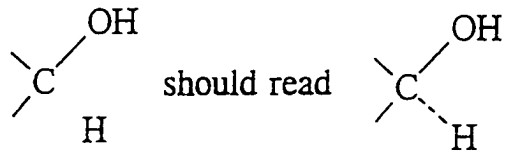
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Columns 48 and 49-50, in the table in Example 6C, for each of Compound Nos. 6C-1 through 6C-11, under column "Z", at each occurrence,



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

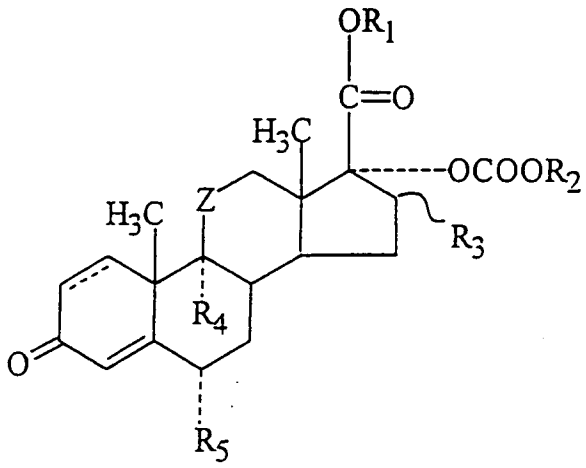
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 50, lines 33-45, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

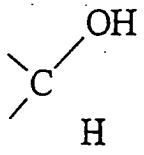
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

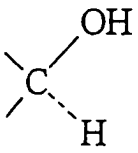
PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Columns 50 through 56, in the table in Example 7A, for each of Compound Nos. 7A-1 through 7A-18 and 7A-21 through 7A-30, under column "Z", at each occurrence,



should read



In Column 55, line 20, "17β-ethoxycarbonyloxy" should read --17α-ethoxycarbonyloxy--.

In Column 56, line 14, "methylandrost" should read --methylandrosta--.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

Staple Here Only !

PRINTER'S TRIM LINE

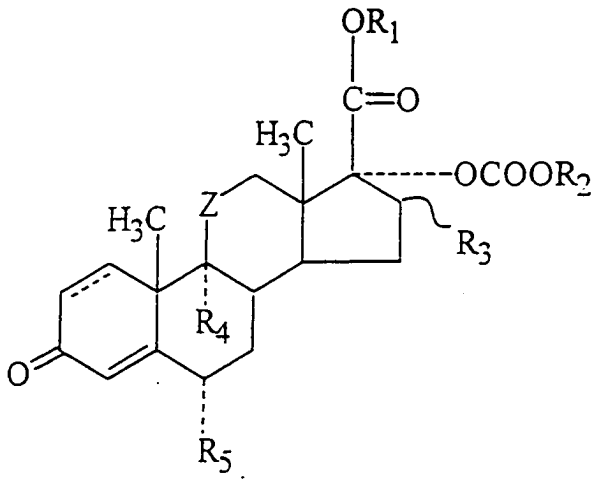
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 56, lines 46-56, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

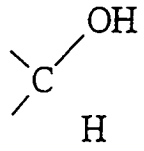
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

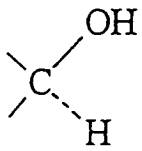
PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Columns 56 through 66, in the table in Example 7B, for each of Compound Nos. 7B-1 through 7B-7, 7B-14 through 7B-18, 7B-22 through 7B-29, 7B-33 through 7B-40, and 7B-44 through 7B-64, under column "Z", at each occurrence,



should read



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

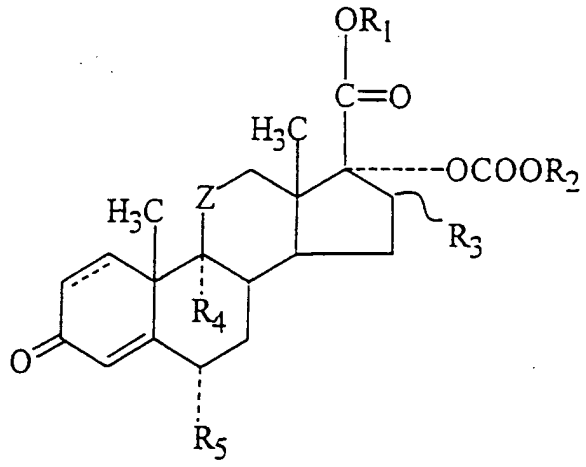
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 66, lines 40-50, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

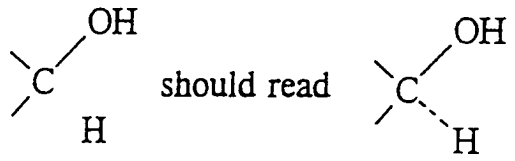
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Columns 66 through 68, in the table in Example 7C, for each of Compound Nos. 7C-1 through 7C-13, under column "Z", at each occurrence,



In Column 69, line 39, "11α," should read –11β,–.

MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of addl copies @ 50¢ per page

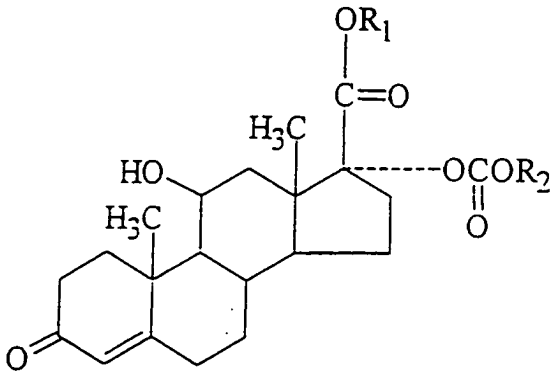
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 69, lines 52-62, delete the structural formula and insert in its stead:



In Column 70, lines 3-13, delete the structural formula.

In Column 70, line 31, "thylfulfonylmethyl" should read --thylsulfonylmethyl--.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

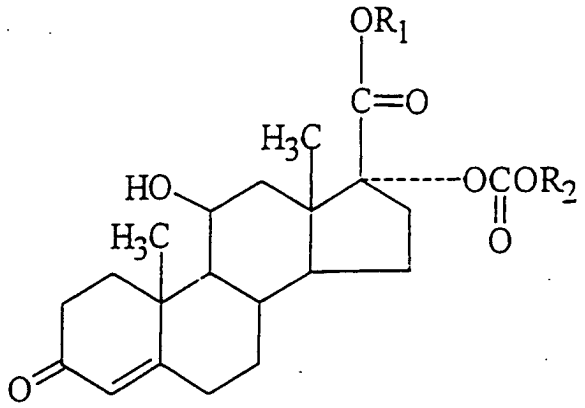
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 70, lines 37-46, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

Staple Here Only !

PRINTER'S TRIM LINE

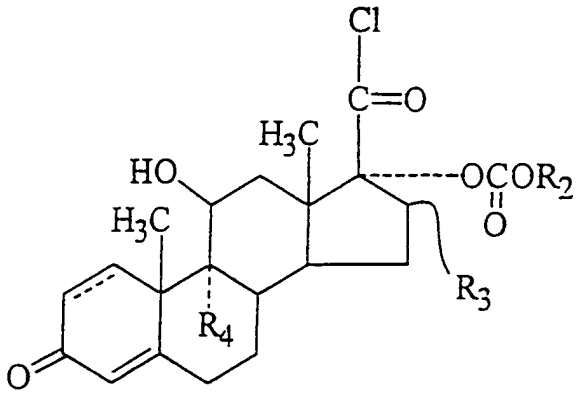
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 71, lines 2-11, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

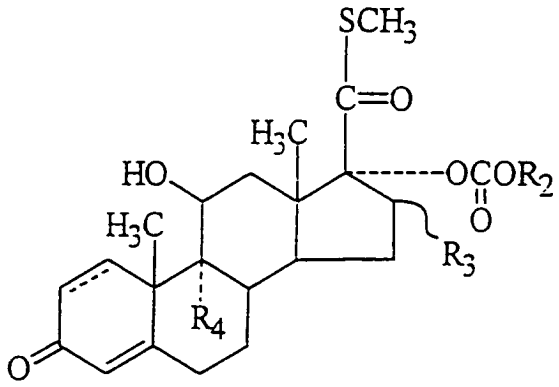
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 71, lines 22-31, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

No. of addt'l copies @ 50¢ per page

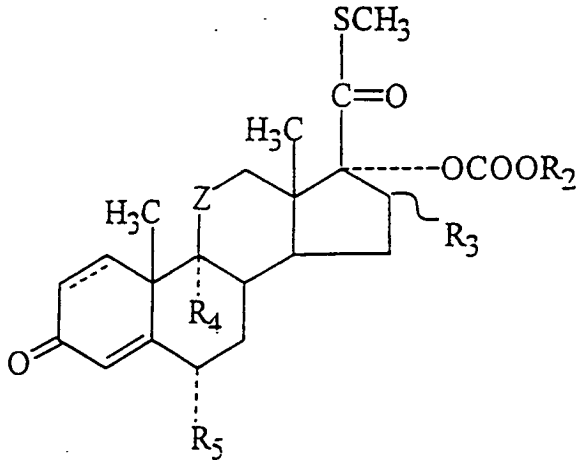
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 71, lines 44-54, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

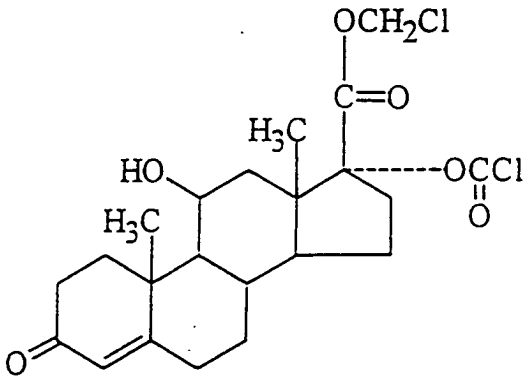
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 72, lines 5-13, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

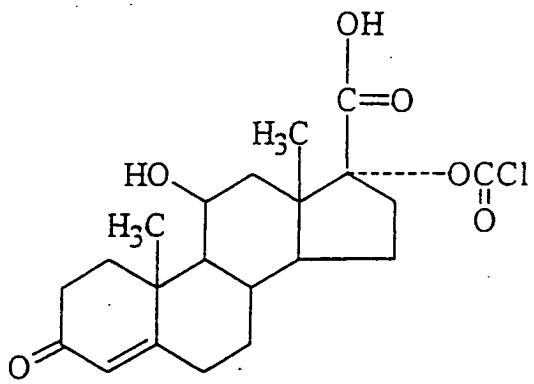
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 72, lines 51-60, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

Staple Here Only !

PRINTER'S TRIM LINE

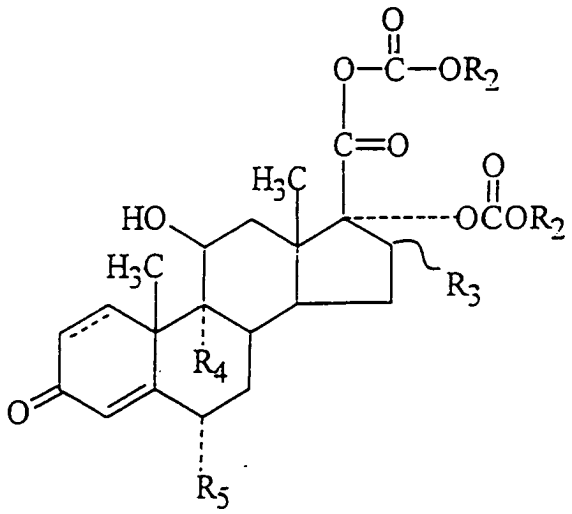
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 74, lines 2-14, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

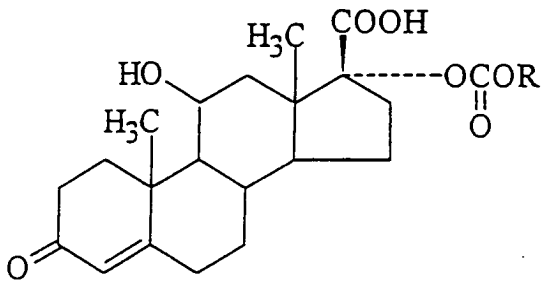
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 74, lines 47-55, delete the structural formula and insert in its stead:



In Column 76, line 6, "dikmethylpyrrolidine" should read --dimethylpyrrolidine--.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

'Staple Here Only !

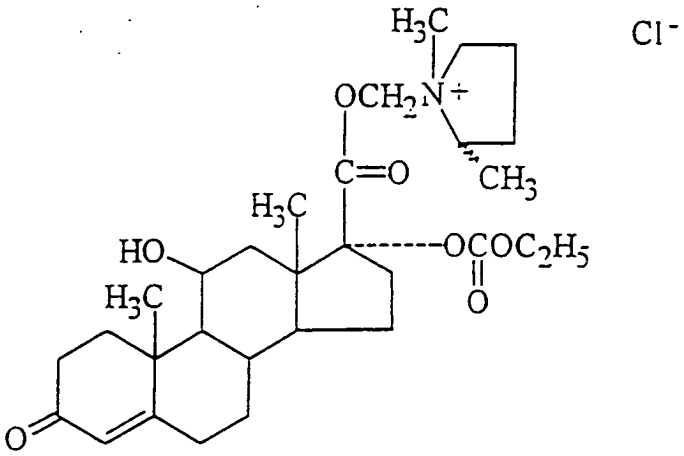
PRINTER'S TRIM LINE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 76, lines 17-30, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

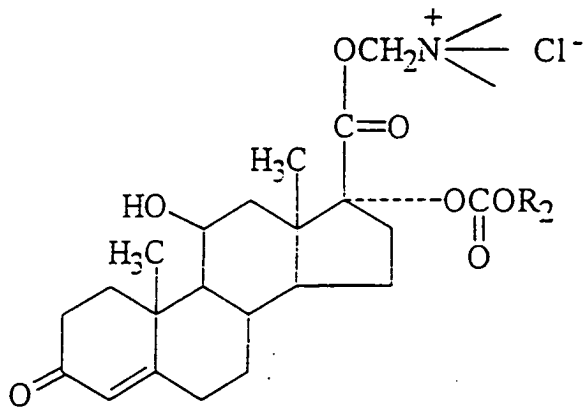
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 76, lines 37-48, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

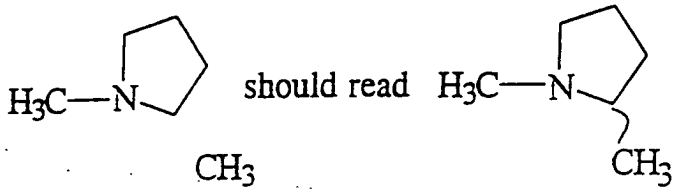
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

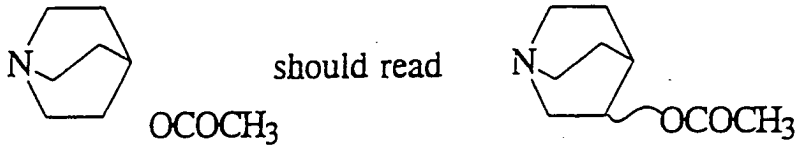
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 76, lines 52-55,



In Column 77, lines 3-12, delete the structural formula.

In Column 77, lines 17-20,



In Column 77, lines 57-58, "Benalkonium" should read --Benzalkonium--.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

FORM PTO 1050 (Rev. 2-93)

UNITED STATES PATENT AND TRADEMARK OFFICE

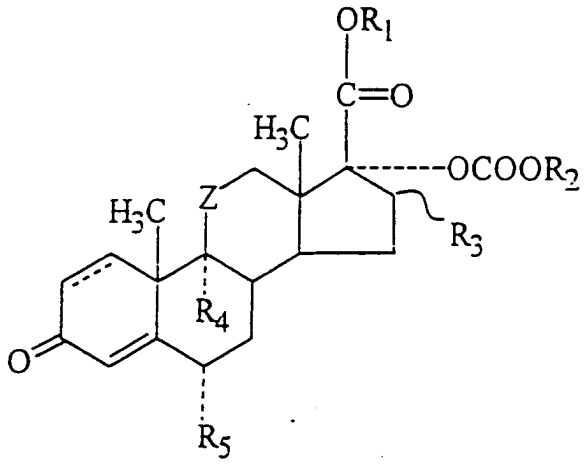
CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 78, line 38, "Eye Drops" should be underlined.

In Column 79, lines 14-25, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

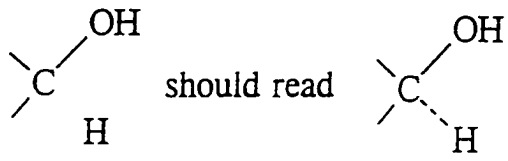
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Columns 79-80, lines 24-38, in the table in Example 29, for each of Compound Nos. 29-1 and 29-2, under column "Z", at each occurrence,



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

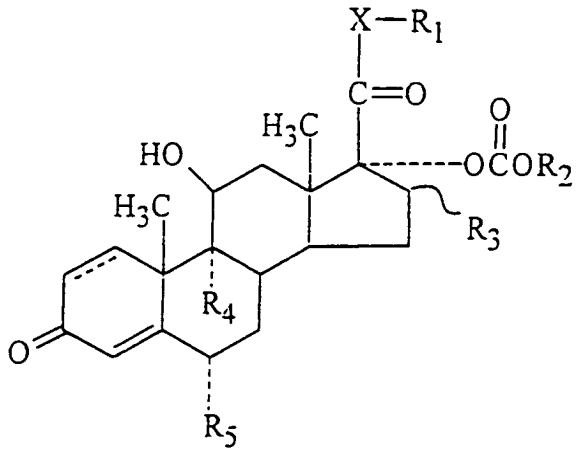
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 80, lines 2-12, part (a) of Claim 1, delete the structural formula (I) and insert in its stead:



(I)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

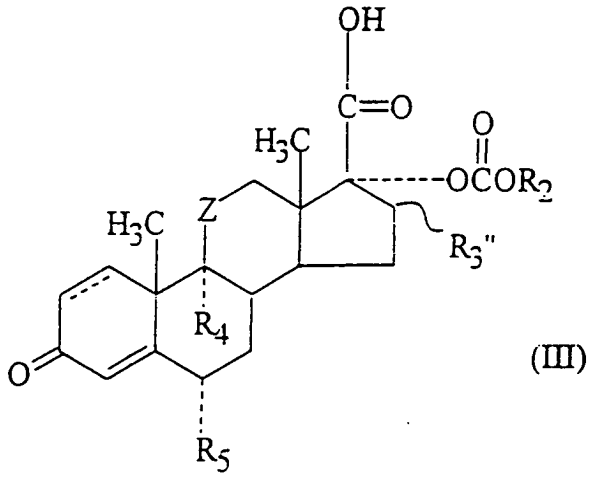
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 81, lines 55-65, part (c) of Claim 1, delete the structural formula and insert in its stead:



(III)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

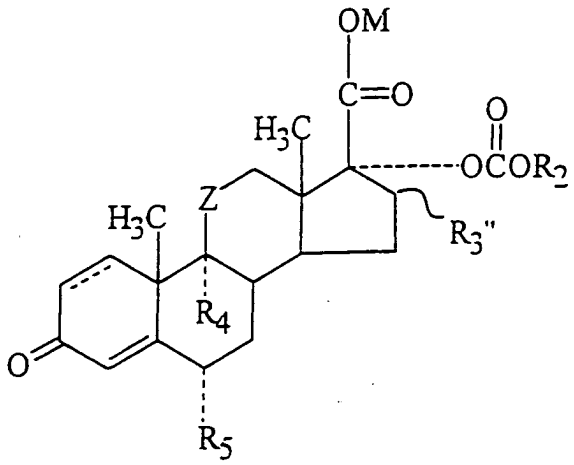
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 82, lines 15-24, part (d) of Claim 1, delete the structural formula (IV) and insert in its stead:



(IV)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

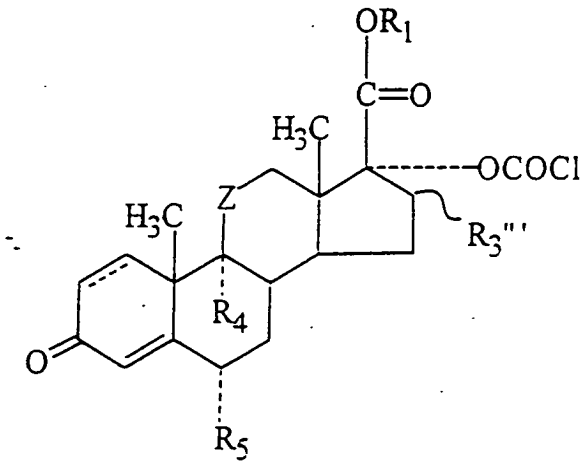
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 82, lines 34-44, part (e) of Claim 1, delete the structural formula (VII) and insert in its stead:



(VII)

MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

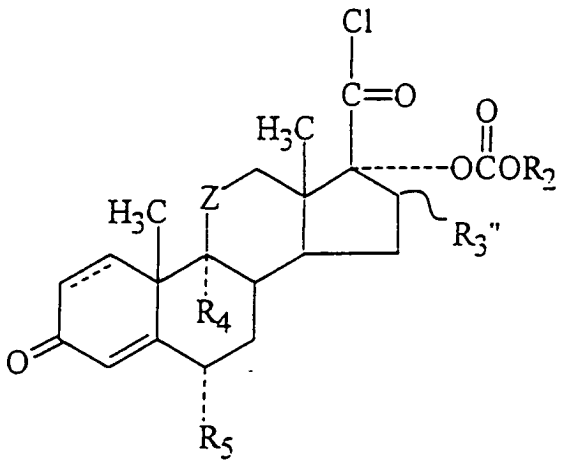
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 82, lines 53-64, part (f) of Claim 1, delete the structural formula (VIII) and insert in its stead:



(VIII)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

Staple Here Only !

PRINTER'S TRIM LINE

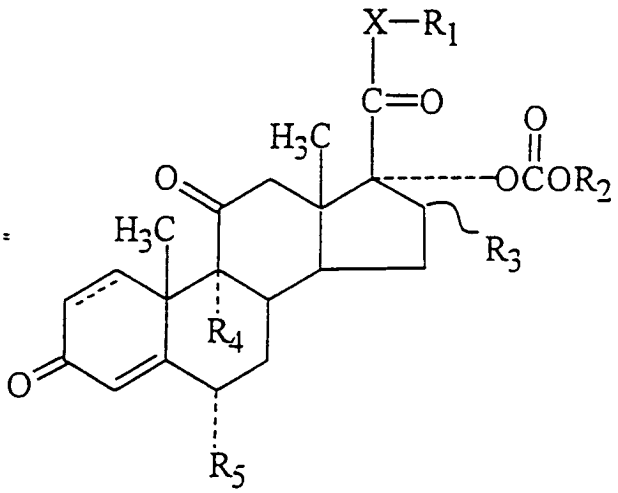
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 83, lines 2-12, part (g) of Claim 1, delete the structural formula (IX) and insert in its stead:



(IX)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of addt'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

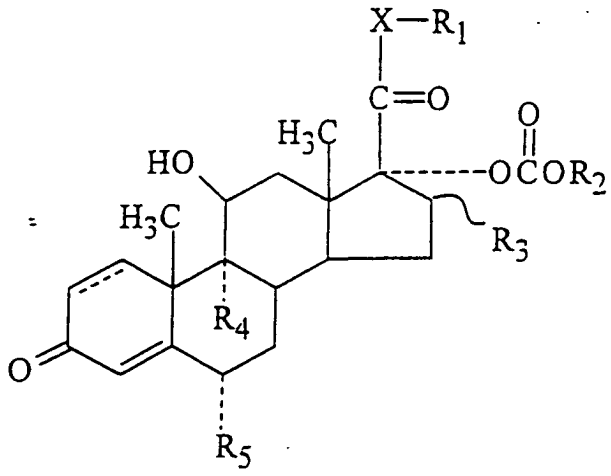
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 83, lines 20-31, part (a) of Claim 2, delete the structural formula (I) and insert in its stead:



(I)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

UNITED STATES PATENT AND TRADEMARK OFFICE

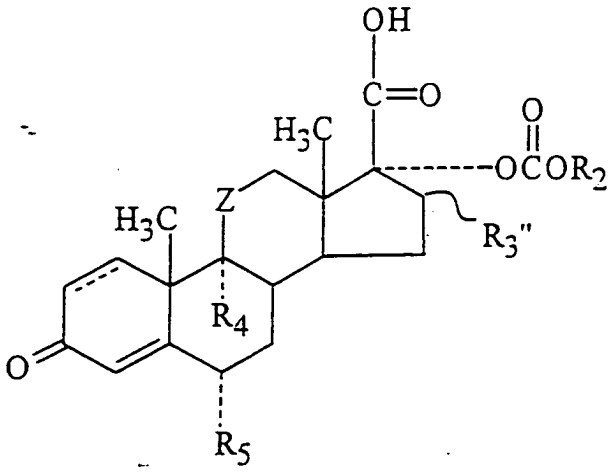
CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 83, line 49, part (a) of Claim 2, in the definition of R_3, "β-methyl, β-methyl" should read –α-methyl, β-methyl–.

In Column 84, lines 2-13, part (c) of Claim 2, delete the structural formula (III) and insert in its stead:



(III)

MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

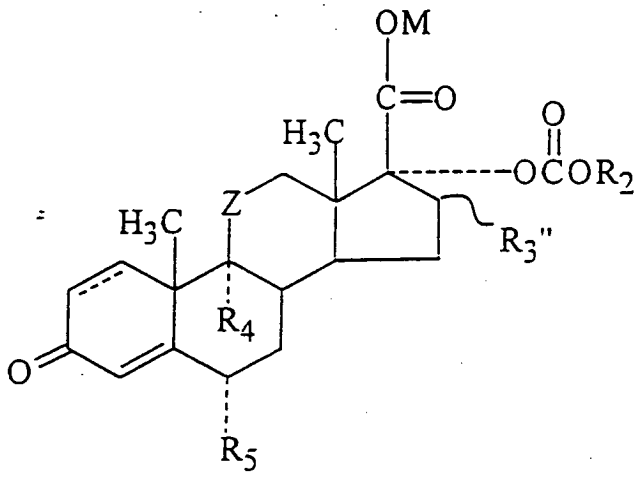
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 84, lines 31-43, part (d) of Claim 2, delete the structural formula (IV) and insert in its stead:



(IV)

MAILING ADDRESS OF SENDER:

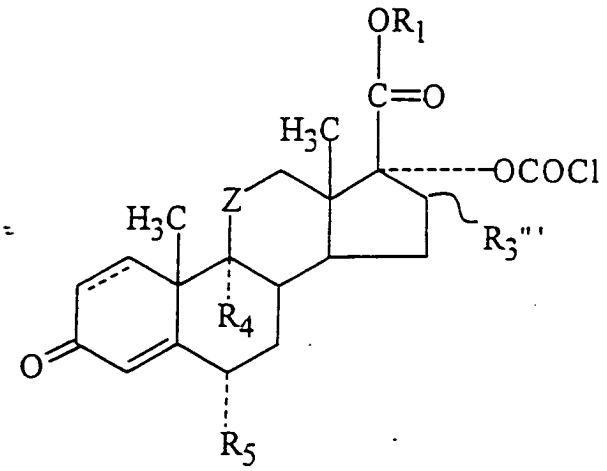
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 84, lines 51-62, part (e) of Claim 2, delete the structural formula (VII) and insert in its stead:



(VII)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

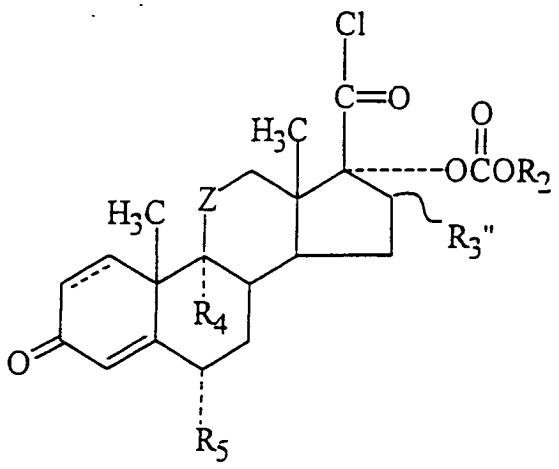
No. of add'l copies @ 50¢ per page

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 85, lines 2-12, part (f) of Claim 2, delete the structural formula (VIII) and insert in its stead:



(VIII)

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

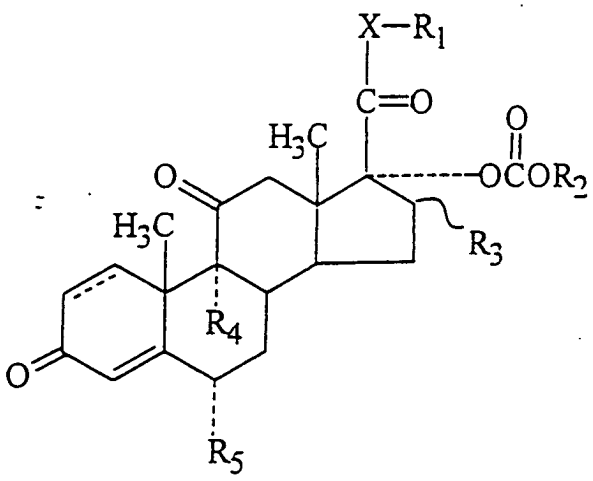
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 85, lines 18-28, part (g) of Claim 2, delete the structural formula (IX) and insert in its stead:



(IX)

In Column 87, line 16, Claim 50, "sentss" should read --sents--.

MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

Staple Here Only !

PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 88, line 42, Claim 73, after "claim 2" and before "is", insert –which–.

In Column 89, line 24, Claim 86, "dien" should read –diene–.

In Column 89, line 53, Claim 95, delete "-I-" and insert – -O- –.

MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

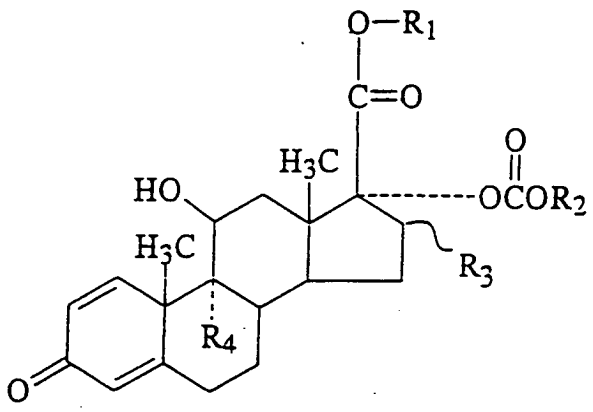
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 90, lines 33-42, Claim 110, delete the structural formula and insert in its stead:



MAILING ADDRESS OF SENDER:

Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

PATENT NO. 4,996,335

No. of add'l copies @ 50¢ per page

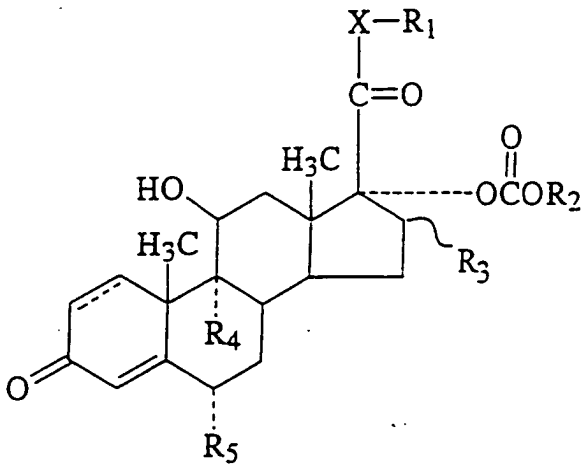
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,996,335
DATED : February 26, 1991
INVENTOR(S) : Nicholas S. BODOR

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 90, lines 52-63, Claim 113, delete the structural formula (I) and insert in its stead:



(I)

MAILING ADDRESS OF SENDER:
Norman H. Stepno
Burns, Doane, Swecker & Mathis, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

No. of addl copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

K

75L9/0908

NORMAN H. STEPNO
BURNS, DOANE, SWECKER & MATHIS
GEORGE MASON BLDG.
WASHINGTON & PRINCE STS., P. O. BOX 1404
ALEXANDRIA, VA 22313-1404

DATE MAILED
09/08/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,996,335	283	465	----	06/807,034	02/26/91	12/09/85	04	YES	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	003800-000

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

BODOR
MEB

PTO! 439 (REV 4 88)

HGP Inc

(904) 462-5232
FAX (904) 462-5236

One Progress Blvd. • Box 36 • Alachua, Florida, 32615

December 1, 1988

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

INITIAL IND SUBMISSION FOR P-5604

Dear Sirs:

Enclosed please find an original and two copies of our IND submission for our novel ophthalmic steroid P-5604.

HGP Inc is a new company, formed in 1987 but operating through subcontracts and an overseas sponsor. HGP Inc was set up with a formal staff on October 1st 1988 with the purpose of filing IND's and initiating studies in the U.S.A. Much of the work included in the submission was carried out in the United Kingdom under the sponsorship of Ethical Pharmaceuticals Ltd. Prior to October of this year, management of the project in the U.S. was handled by Pharmatec, Inc. of Alachua Florida.

All toxicology studies reported in this IND were carried out under GLP conditions and the U.K. clinical study was carried out to GCP standards.

A series of amendments to this IND will follow and will include details of the stability studies on the proposed clinical formulation and full details of the recently completed British Phase I study.

Should you require additional information please contact me at (904) 462-5232

Cordially,
HGP Inc

John F. Howes

John F. Howes, Ph.D.
Vice President for Development.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: November 30, 1987.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1 NAME OF SPONSOR
HGP Inc

2 DATE OF SUBMISSION
12/01/88

3. ADDRESS (Number, Street, City, State and Zip Code)
One Progress Boulevard
Box 36
Alachua, FL 32615

4. TELEPHONE NUMBER (Include Area Code)
(904) 462-5232

5 NAME(S) OF DRUG (Include all available names. Trade, Generic, Chemical, Code)
P-5604

6. IND NUMBER (If previously assigned)

7 INDICATION(S) (Covered by this submission)
Ophthalmic Steroidal Anti-inflammatory

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☒ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ (Specify)

9 LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420) AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

None

10 SERIAL NUMBER: 0 0 0

IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (i.e., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

11 THIS SUBMISSION CONTAINS THE FOLLOWING (Check all that apply)

☒ INITIAL INVESTIGATIONAL NEW DRUG

PROTOCOL AMENDMENT(S)
- ☐ NEW PROTOCOL
- ☐ CHANGE IN PROTOCOL
- ☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S)
- ☐ CHEMISTRY/MICROBIOLOGY
- ☐ PHARMACOLOGY/TOXICOLOGY
- ☐ CLINICAL

IND SAFETY REPORT(S):
- ☐ INITIAL WRITTEN
- ☐ FOLLOW-UP TO

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ PRES

☐ GENERAL CORRESPONDENCE ☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER (Specify)

Refer to the designated CFR citations before checking any of the following.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION

FOR FDA USE ONLY

CONSOLIDATED RECEIPT STAMP	FDA RECEIPT STAMP	IND NUMBER ASSIGNED
		DIVISION ASSIGNMENT

FORM FDA 1571 (4/87) PREVIOUS EDITION IS OBSOLETE

CONTENTS OF APPLICATION

This application contains the following items: *(check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- ☒ 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- ☒ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- ☒ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- ☒ 5 Investigator's brochure *[21 CFR 312 23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312 23 (a) (6)]*
  - ☒ a. Study protocol(s) *[21 CFR 312 23 (a) (6)]*
  - ☒ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☒ c. Facilities data *[21 CFR 312 23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☒ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- ☒ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - ☒ a. Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- ☒ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- ☒ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- ☒ 10. Additional information *[21 CFR 312 23 (a) (10)]*

11. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED

12. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

John F. Howes Vice President for Development

13. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

John F. Howes Vice President for Development
Edwin Keates, M.D. Acting Medical Director

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND or on earlier notification by FDA. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE
John F. Howes	John F Howes

18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
One Progress Blvd. Box 36 Alachua, FL 32615	(904) 462-5232	12/01/88

(WARNING: A willfully false statement is a criminal offense U S C Title 18, Sec. 1001.)

• U S GPO 1987-O-181-338/64882

2 Innovation Drive
Alachua, FL 32615
TEL 904-462-1210
FAX 904-462-5401

PHARMOS

March 18, 1998

Joanne Holmes
FDA, Division of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products
HFD 550
9201 Corporate Blvd
Rockville, MD 20850

RE: IND 32,432

Dear Ms. Holmes:

This letter provides confirmation that, the following personnel listed below at Bausch & Lomb Pharmaceuticals are authorized by Pharmos to contact the FDA on all prior and future issues concerning the above referenced IND.

Christine Simmons, Director, Regulatory Affairs
Cal Bowman, Vice President, Regulatory Affairs
Ellen Strahlman, M.D., Director of Corporate Medical Affairs

The purpose of this authorization is to facilitate the interchange of data and regulatory information on this program between B & L Pharmaceuticals and the FDA, without the necessity of referencing Pharmos each time. All amendments to the IND will continue to be handled by Pharmos Corp.

If you have any questions please do not hesitate to contact me at 904-462-1210 (phone) or 904-462-5401 (fax).

Sincerely,

John F. Howes, Ph.D.
Vice President,
Clinical and Regulatory Affairs
JFH:sg

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

M

IND 32,432

HGP Inc
One Progress Boulevard
Box 36
Alachua, FL 32,615

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 32,432

Sponsor: HGP Inc.

Name of Drug: P-5604

Date of Submission: 12/01/88

Date of Receipt: December 2, 1988

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

U.S. GOVERNMENT PRINTING OFFICE-1984-447-553/7406

IND 32,432

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

Should you have any questions concerning this IND, please call:

Consumer Safety Officer Maria Rossana R. Cook
(301) 443- 0257

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Center for Drugs and Biologics, HFN-815
Attention: DOCUMENT CONTROL ROOM (12B-30)
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drugs and Biologics

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228e (6/84)

U.S. GOVERNMENT PRINTING OFFICE: 1984 - 446-900/7357

2 Innovation Drive
Alachua, FL 32615
TEL 904-462-1210
FAX 904-462-5401

PHARMOS

March 29, 1995

Food and Drug Administration
Center for Drugs and Biologics
Central Document Room
Park Building, Room 214
12420 Parklawn Drive,
Rockville, MD 20852

Re: NDA 20-583

Dear Sirs,

Attached is a full copy of our NDA submission for Loteprednol Etabonate 0.5% Ophthalmic Suspension.

Volumes 2, 3, 4, 16 and 17 were submitted as a Presubmission on January 27th, 1995.

Attached to Volume I are the following items:

- Form 356h
- Cover letter
- Patent Information
- Letter of authorization
- Debarment Statement
- Index to full NDA
- Guide to reviewers to locate, reports, and CV's of personnel involved in the submission.

Under the Prescription Drug Users Fee Act of 1992, Pharmos Corporation has been designated as eligible for the Small Business Exception. The letter confirming this is attached.

For further information please contact me at the following numbers

904-462-1210 (phone)
904-462-5236 (fax)

Sincerely,

John F. Howes

John F. Howes, Ph.D.
Vice President Clinical and Regulatory Affairs

JFH:sg

01 003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 2.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
PHARMOS CORPORATION

DATE OF SUBMISSION
arch 29, 1995

TELEPHONE NO. (Include Area Code)
(904) 462-1210

ADDRESS (Number, Street, City, State and Zip Code)
2 INNOVATION DRIVE
SUITE A
ALACHUA, FL 32615

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-582

DRUG PRODUCT

ESTABLISHED NAME (e.g. USP/USAN)	PROPRIETARY NAME (If any)
LOTEPREDNOL ETABONATE	LOTEMAX

CODE NAME (If any)	CHEMICAL NAME
P-5604	Chloromethyl-17 -ethoxycarbonyloxy-11ß-hydroxyandrosta-1,4-diene-3-one-17ß carboxylate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
OPHTHALMIC SUSPENSION	TOPICAL (ocular)	0.5% w/v

PROPOSED INDICATIONS FOR USE
OPHTHALMIC INFLAMMATION AND ALLERGIC CONDITIONS

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND 32,432
DMF 11105
DMF 11264
DMF 11226

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
N/A	N/A

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g. Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

FORM FDA 356h (10/93) PREVIOUS EDITION IS OBSOLETE.

01 001

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

✓	1. Index
✓	2. Summary (21 CFR 314.50 (c))
✓	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
✓	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
✓	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
✓	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
✓	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
✓	7. Microbiology section (21 CFR 314.50 (d) (4))
✓	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
✓	10. Statistical section (21 CFR 314.50 (d) (6))
✓	11. Case report tabulations (21 CFR 314.50 (f) (i))
✓	12. Case reports forms (21 CFR 314.50 (f) (1))
✓	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
✓	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
✓	15. OTHER *(Specify)* Debarment Statement

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
J.F. Howes	John F. Howes	March 29, 19

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
2 Innovation Drive, Suite A Alachua, FL 32615	(904) 462-1210

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FORM FDA 356h (10/93)

01 002

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-583

FEB 17 1998

Bausch & Lomb
Attention: Christine Simmons, Pharm.D
Director, Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Dr. Simmons:

We acknowledge your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lotemax® (loteprednol etabonate ophthalmic suspension), 0.5%

Therapeutic Classification: Standard

Date of Application: March 29, 1995

Date of Receipt: April 10, 1995

Our Reference Number: 20-583

Your application was filed under section 505(b) of the Act on June 9, 1995, in accordance with 21 CFR 314.101(a).

Sincerely,

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Pharmaceutical Division | 8500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

January 31, 1997

BAUSCH & LOMB
Healthcare and Optics Worldwide

Ms. Peggy Hair
Central Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852

RE: ORIGINAL NEW DRUG APPLICATION
NDA 20-803
Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Dear Ms. Hair:

Pursuant to 21 CFR 314.50, Pharmos Corporation hereby submits a new drug application for loteprednol etabonate ophthalmic suspension, 0.2% , for the treatment of the signs and symptoms of seasonal allergic conjunctivitis.

This submission is contained in 35 volumes. Enclosed is an archival copy and a review copy of the application. Please see the Summary Section (Section 2) for general NDA information and certification statements.

Pharmos has been granted a deferral of payment of the application user fee for one year from the date of submission under the small business exception to the User Fee Act. A copy of the letter granting the deferral and the User Fee Cover Sheet follow the Form 356(h).

A trade name for this product has not yet been identified. It will be submitted to the agency as soon as a name is selected.

All manufacturing sites identified in this application are ready for an FDA inspection.

If you have any questions regarding this information, I may be contacted at the above address or by phone at 813/975-7775. I have been authorized by Pharmos to communicate with FDA on their behalf with regard to this new drug application as indicated in a letter to Ms. Joanne Holmes on January 10, 1997. A copy of the letter follows the User Fee Cover Sheet.

Sincerely,

C. Christine Simmons, Pharm.D
Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmos Corporation	01/31/97
ADDRESS *(Number, Street, City, State and ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
2 Innovation Drive Alachua, FL 32615	(904) 462-1210
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* 20-803 (preassigned)

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Loteprednol etabonate	None

CODE NAME *(If any)*	CHEMICAL NAME
Loteprednol etabonate 0.2% Loteprednol etabonate allergy Core 353	See package insert

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTHS (S)
Sterile Suspension	Ophthalmic	0.2%

PROPOSED INDICATIONS FOR USE

For the treatment of the signs and symptoms of seasonal allergic conjunctivitis

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

NDA 20-583
DMF 1466
DMF 4251
DMF 1528
DMF 1584

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Summary (21 CFR 314.50) (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
X	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
X	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
X	12. Case reports forms (21 CFR 314.50 (f) (1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Christine Simmons, Pharm. D.	Christine Simmons	1-29-97

ADDRESS *(Street, City, State, ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
8500 Hidden River Parkway Tampa, FL 33637	(813) 975-7775

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-803

FEB 12 1997

Pharmos Corporation
Attention: C. Christine Simmons, Pharm. D.
Director, Regulatory Affairs
2 Innovation Drive
Alachua, FL 32615

Dear Dr. Simmons:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Loteprednol Etabonate Ophthalmic Suspension, 0.2%

Therapeutic Classification: Standard

Date of Application: January 31, 1997

Date of Receipt: February 3, 1997

Our Reference Number: 20-803

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 4, 1997, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

for

Lissante C. LoBianco
Acting Supervisor Consumer Safety Officer
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

2 Innovation Drive
Alachua, FL 32615
TEL 904-462-1210
FAX 904-462-5401

PHARMOS

January 10, 1997

Joanne Holmes
FDA, Division of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products
HFD 550
9201 Corporate Blvd.
Rockville, MD

RE: NDA 20-803

Dear Ms. Holmes:

The following individuals are hereby authorized to act on behalf of Pharmos with respect to communications and regulatory submissions to FDA in connection with NDA Reference No. 20-803, including submission under 21 CFR Part 314.

Christine Simmons, Director, Regulatory Affairs
Cal Bowman, Vice President, Regulatory Affairs
Ellen Strahlman, M.D., Director of Corporate Medical Affairs

The purpose of this authorization is to facilitate the interchange of data and regulatory information on this program between B & L Pharmaceuticals and the FDA, without the necessity of referencing Pharmos each time.

If you have any questions, please do not hesitate to contact me at 904-462-1210 (phone) or 904-462-5401 (fax).

Sincerely,

Gad Riesenfeld, Ph.D.
Executive Vice President
Chief Operating Officer

GR/amm

33 Wood Avenue South, Ste. 466
Iselin, New Jersey 08830
TEL 732-603-3526
FAX 732-603-3532

PHARMOS

Ms. Anna Wysowskyj
Bausch & Lomb Pharmaceutical Division
8500 Hidden River Parkway
Tampa, FL 33637

Re: *Loteprednol Etabonate ("LE")*

Dear Anna:

Pharmos Corporation, a Nevada corporation (the "Company"), hereby authorizes Bausch & Lomb Inc., and its affiliates (including without limitation Bausch & Lomb Pharmaceuticals, Inc.) to communicate with the US Food and Drug Administration on the Company's behalf in connection wit the following files relating to LE:

IND 32,432; NDA 20-583; NDA 20-803 and NDA 20-841.

This authorization is subject to your sending us copies of all communications you make on the Company's behalf and your contacting the Company prior to any communication relating to significant or material matters affecting LE or the Company.

If you have any questions, please do not hesitate to call.

Sincerely,

PHARMOS CORPORATION

By: G. Riesenfeld

Gad Riesenfeld, Ph.D.
President & Chief Operating Officer

Pharmaceutical Division
3500 Hidden River Parkway
Tampa FL 33637
813 975 7700
Fax 813 975 7770

P

BAUSCH & LOMB
Healthcare and Optics Worldwide

March 7, 1997

Ms. Peggy Hair
Central Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852

RE: ORIGINAL NEW DRUG APPLICATION (preassigned NDA 20-841)
Loteprednol Etabonate Ophthalmic Suspension, 0.5%
New Indication: Post-Operative Inflammation Following Ocular Surgery

Dear Ms. Hair:

Pursuant to 505(b)(1) of the Federal Food Drug and Cosmetic Act, Pharmos hereby submits a new drug application for loteprednol etabonate ophthalmic suspension, 0.5%, indicated for the treatment of post-operative inflammation following ocular surgery. Another new drug application (NDA 20-583) is currently under review by the agency for this same drug product indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye, including anterior uveitis.

For ease of review, the data to support the indication sought under this NDA are being submitted in an amendment to NDA 20-583. Thus, the integrated summaries of efficacy information and safety data in that amendment as well as the proposed labeling will incorporate the information from all studies conducted thus far with loteprednol etabonate ophthalmic suspension, 0.5%. NDA 20-583 is referenced in support of this new drug application.

Pharmos has been granted a deferral of payment of the application user fee for one year from the date of submission under the small business exception to the User Fee Act. A copy of the letter granting the deferral and the User Fee Cover Sheet follow the Form 356(h).

Please let me know if you have any comments or questions about this information. I can be reached by telephone at 813/975-7775 or by fax at 813/975-7757. I have been authorized by Pharmos to communicate with FDA on their behalf with regard to this new drug application as indicated in a letter to Ms. Joanne Holmes on February 25, 1997. A copy of the letter to Ms. Holmes follows the letter granting the small business exception to the Prescription Drug User Fee Act.

Best Regards,

Christine Simmons

Christine Simmons, Pharm.D
Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314).*

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmos Corporation	March 7, 1997
ADDRESS *(Number, Street, City, State and ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
2 Innovation Drive Alachua, FL 32615	904 462-1210
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* 20-841

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Loteprednol etabonate	Lotemax

CODE NAME *(If any)*	CHEMICAL NAME

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Sterile Suspension	Ophthalmic	0.5%

PROPOSED INDICATIONS FOR USE

Post-operative inflammation following ocular surgery.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

NDA 20-583

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50) (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Christine Simmons, Pharm. D.	Christine Simmons	3-7-97
ADDRESS *(Street, City, State, ZIP Code)* 8500 Hidden River Parkway Tampa, FL 33637		TELEPHONE NO. *(Include Area Code)* (813) 975-7775

WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FORM FDA 356h (5/95) PREVIOUS EDITION IS OBSOLETE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 17 1997

NDA 20-841

Pharmos Corporation
Attention: Christine Simmons, Pharm.D
Director, Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Dr. Simmons:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%

Therapeutic Classification: Standard

Date of Application: March 7, 1997

Date of Receipt: March 10, 1997

Our Reference Number: 20-841

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 9, 1997 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Joanne Holmes, Clinical Reviewer, at 301-827-2090.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

Lissante C. LoBianco
Acting Supervisor Project Manager
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

2 Innovation Drive
Alachua, FL 32615
TEL 904-462-1210
FAX 904-462-5401

PHARMOS

February 24, 1997

Joanne Holmes
FDA, Division of Analgesic, Anti-inflammatory
and Ophthalmologic Drug Products
HFD 550
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-841

Dear Ms. Holmes:

This letter provides confirmation that the following personnel listed below at Bausch & Lomb Pharmaceuticals are authorized by Pharmos to contact the FDA on all prior and future issues concerning the above referenced NDA.

Christine Simmons, Director, Regulatory Affairs
Ellen Strahlman, M.D. Director of Corporate Medical Affairs

The purpose of this authorization is to facilitate the interchange of data and regulatory information on this program between B & L Pharmaceuticals and the FDA without the necessity of referencing Pharmos each time.

If you have any question, please do not hesitate to contact me at 904 462 1210 or 904 462 5401 (fax).

Sincerely,

G. Riesenfeld

Gad Riesenfeld, Ph.D.
President, Chief Operating Officer

cl

33 Wood Avenue South, Ste. 466
Iselin, New Jersey 08830
TEL 732-603-3526
FAX 732-603-3532

PHARMOS

Ms. Anna Wysowskyj
Bausch & Lomb Pharmaceutical Division
8500 Hidden River Parkway
Tampa, FL 33637

Re: *Loteprednol Etabonate ("LE")*

Dear Anna:

Pharmos Corporation, a Nevada corporation (the "Company"), hereby authorizes Bausch & Lomb Inc., and its affiliates (including without limitation Bausch & Lomb Pharmaceuticals, Inc.) to communicate with the US Food and Drug Administration on the Company's behalf in connection wit the following files relating to LE:

IND 32,432; NDA 20-583; NDA 20-803 and NDA 20-841.

This authorization is subject to your sending us copies of all communications you make on the Company's behalf and your contacting the Company prior to any communication relating to significant or material matters affecting LE or the Company.

If you have any questions, please do not hesitate to call.

Sincerely,

PHARMOS CORPORATION

By: G. Riesenfeld

Gad Riesenfeld, Ph.D.
President & Chief Operating Officer

FDA Correspondence Log
for the period 12/01/88 to 01/27/95

IND 32,432 loteprednol etabonate ophthalmic suspension

Date	From[1]	To[1]	Via	Subject
12/1/88	HGP	FDA	Letter	IND 32,432 filed for loteprednol etabonate ophthalmic suspension.
undated	FDA	HGP	Letter	Acknowledgement that IND 32.432 was received by FDA on 2/1/88.
12/14/88	HGP	FDA	Letter	IND Correspondence No. 001: Stability update.
1/3/89	HGP	FDA	Letter	IND Correspondence No. 002: Response to request for manufacturing information.
1/30/89	HGP	FDA	Letter	IND Correspondence No. 003: Stability update.
4/24/89	HGP	FDA	Letter	IND Correspondence No. 004: Stability update.
6/16/89	HGP	FDA	Letter	IND Correspondence No. 005: Response to request for information on stability test methods.
8/7/89	HGP	FDA	Letter	IND Correspondence No. 006: Study protocol.
8/8/89	HGP	FDA	Letter	IND Correspondence No. 007: Study report PHA-21.
9/29/89	HGP	FDA	Letter	IND Correspondence No. 008: Response to request for information on labeling.
10/23/89	HGP	FDA	Letter	IND Correspondence No. 009: Study report PHA-22 and stability update.
1/17/90	Xenon	FDA	Letter	IND Correspondence No. 010: IND annual report and new Investigator's Brochure.
3/7/90	Xenon	FDA	Letter	IND Correspondence No. 011: Amendment to Study 104 protocol.
3/16/90	Xenon	FDA	Letter	IND Correspondence No. 012: Additional 0.5% and 0,1% formulations.
4/10/90	Xenon	FDA	Letter	IND Correspondence No. 013: New 0.5% formulation.
4/11/90	Xenon-Reaves	FDA-Nazario	Phone	Discussion concerning Dr. Wiley Chambers' recommendations for the design of Lotemax clinical trials.
5/11/90	Xenon	FDA	Letter	IND Correspondence No. 014: Amendment to Study 104 protocol - Conjunctival Provocation Test.
7/6/90	Xenon	FDA	Letter	IND Correspondence No. 015: Study reports PTC 46, 48, 51, and 67.
8/10/90	Xenon	FDA	Letter	IND Correspondence No. 016: New 0.5% formulation.
8/17/90	Xenon-Reaves	FDA-Huntley	Phone	Discussion concerning enrollment of women in Lotemax clinical trials.

[1] HGP - HGP, Inc.
Xenon - Xenon Vision (formerly HGP, Inc.)
Pharmos - Pharmos Corporation (formerly Xenon Vision)
B&L - Bausch & Lomb Pharmaceuticals, Inc., authorized agent for Pharmos Corporation

FDA Correspondence Log
for the period 12/01/88 to 01/27/95

Date	From[1]	To[1]	Via	Subject
8/30/90	Xenon	FDA	Letter	IND Correspondence No. 017: Amendments to Study 103 protocol. Protocols for Studies 105 and 106.
9/5/90	Xenon	FDA	Letter	IND Correspondence No. 018: General.
10/11/90	Xenon	FDA	Letter	IND Correspondence No. 019: Amendments to protocols for Studies 103 and 105. Additional 1572s for Studies 103 and 106.
12/5/90	Xenon-Reaves	FDA-Chambers	Phone	Request for FDA recommendations for the development of loteprednol etabonate as a single entity and as a combination product.
12/6/90	Xenon-Reaves	FDA-Chambers	Phone	Discussion concerning Lotemax single entity indications, class labeling, combination products, Phase I & II studies, carcinogenicity requirements, and End of Phase II Meeting.
12/6/90	Xenon	FDA	Letter	IND Correspondence No. 020: Protocols for Studies 112 and 114 - Seasonal Allergic Conjunctivitis.
11/17/91	Xenon	FDA	Letter	IND Correspondence No. 021: Amendment to protocol for Study 103.
1/23/91	Xenon-Reaves	FDA-Huntley	Letter	Request for Lotemax preclinical data review meeting with FDA.
1/23/91	Xenon-Reaves	FDA-Osterberg	Phone	Request for information on the need for chronic carcinogenicity studies for corticosteroids.
1/31/91	Xenon	FDA	Letter	IND Correspondence No. 022: IND Annual Report.
2/12/91	Xenon	FDA	Letter	IND Correspondence No. 023: Pharmacology and toxicology update.
2/26/91	Xenon	FDA	Letter	IND Correspondence No. 024: Pharmacology and toxicology update.
3/6/91	Xenon-Reaves	FDA-Chambers Huntley	Meeting	Informal meeting at FDA to discuss loteprednol etabonate development.
5/21/91	Xenon	FDA	Letter	IND Correspondence No. 025: Additional 1572 for Study 103. CMC information.
7/10/91	Xenon	FDA	Letter	IND Correspondence No. 026: Discontinuation of Study 103.
7/11/91	Xenon-Reaves	FDA-Chambers	Phone	Discussion concerning Study 103.
7/11/91	Xenon-Reaves	FDA-Chambers	Phone	Notification of the discontinuation of Study 103.
12/6/91	Xenon	FDA	Letter	IND Correspondence No. 027: IND Annual Report. Updated Investigator's Brochure.
1/29/92	FDA-Weikel	Xenon-Howes		FDA questions concerning control of drug used in Study 103.
2/3/92	Xenon	FDA	Letter	IND Correspondence No. 028: CMC information related to Study 103.
4/1/92	Xenon-Howes	FDA-Chambers	Memo	Submission of proposed agenda for End of Phase II Meeting.
4/8/92	Xenon	FDA	Letter	IND Correspondence No. 029: Request for an End of Phase II Meeting.

FDA Correspondence Log

for the period 12/01/88 to 01/27/95

Date	From[1]	To[1]	Via	Subject
6/8/92	Xenon-Howes	FDA-Chambers	Letter	Submission of End of Phase II packages, list of planned attendees, and major issues to be discussed.
6/24/92	Xenon	FDA	Letter	IND Correspondence No. 030: Toxicology update. Report for Study PTC 74-91.
7/7/92	Xenon	FDA	Letter	IND Correspondence No. 031: CMC information related to study 103.
7/15/92	Pharmos-Howes	FDA-Chambers	Meeting	End of Phase II FDA meeting.
8/3/92	Pharmos	FDA-Knight	Letter	Submission of revised protocols for two proposed Lotemax Phase III studies.
8/3/92	Xenon-Howes	FDA-Knight	Letter	Desk copies of Lotemax protocols 107, 121, and 122.
8/10/92	Pharmos-Howes	FDA-Knight	Phone	Discussion concerning Lotemax study protocols.
8/10/92	Xenon-Howes	FDA-Knight	Phone	Request for FDA comment on Lotemax protocols 107, 121, 122.
10/15/92	Xenon	FDA	Letter	IND Correspondence No. 032: Protocols for Studies 107 and 108 - Efficacy and Safety Evaluation of Loteprednol Etabonate in Giant Papillary Conjunctivitis
11/13/92	Xenon	FDA	Letter	IND Correspondence No. 033: Name change from Xenon Vision to Pharmos Corporation.
11/13/92	Pharmos	FDA	Letter	IND Correspondence No. 034: Response to questions regarding Study PTC 74-C.
1/14/93	Pharmos-Coultas	FDA-Knight	Letter	Submission of desk copies of Lotemax clinical study 121 protocol for review.
1/29/93	Pharmos	FDA	Letter	IND Correspondence No. 035: IND Annual Report and Updated Investigator's Brochure.
2/4/93	Pharmos-Coultas	FDA-Knight	Phone	Request for information on clinical programs for ophthalmic steroids.
2/4/93	Pharmos-Coultas	FDA-Knight	Phone	Request for information on label claims and the studies needed to support them and requirements for combination products.
3/17/93	Pharmos	FDA	Letter	IND Correspondence No. 036: Amendment to protocol for Study 107. Additional Form 1572 and labeling.
4/5/93	Pharmos-Howes	FDA-Joyce	Letter	Confirmation of 5/12/93 meeting date and Lotemax UK sites and PRK patients as topics.
5/21/93	Pharmos	FDA	Letter	IND Correspondence No. 038: Amendment to protocols for Studies 107 and 108.
5/27/93	Pharmos	FDA	Letter	IND Correspondence No. 039: CMC information.
5/27/93	Pharmos	FDA	Letter	IND Correspondence No. 039: CMC Information
5/28/93	Pharmos	FDA	Letter	IND Correspondence No. 040: FDA meeting minutes
7/8/93	Pharmos	FDA	Letter	IND Correspondence No. 041: Amended Form 1572s for Studies 107 and 108.
7/28/93	Pharmos	FDA	Letter	IND Correspondence No. 042: Protocol for Study 121 - Safety and Efficacy Evaluation of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis

FDA Correspondence Log
for the period 12/01/88 to 01/27/95

Date	From[1]	To[1]	Via	Subject
8/6/93	Pharmos	FDA	Letter	IND Correspondence No. 043: Additional Form 1572s for Study 121.
8/6/93	Pharmos	FDA	Letter	IND Correspondence No. 044: Protocol for Study 122 - Safety and Efficacy Evaluation of Loteprednol Etabonate in Acute Anterior Uveitis
8/3/93	Pharmos-Howes	FDA-Carreras	Phone	Discussion concerning entry criteria for SAC studies.
8/4/93	Pharmos-Howes	FDA-Carreras	Phone	Discussion concerning entry criteria for SAC studies.
8/9/93	Pharmos	FDA	Letter	IND Correspondence No. 045: Response to FDA comments concerning SAC study design.
8/11/93	Pharmos	FDA	Letter	IND Correspondence No. 046: Additional Form 1572s for Study 121.
8/24/93	Pharmos	FDA	Letter	IND Correspondence No. 047: Change of address.
8/31/93	Pharmos	FDA	Letter	IND Correspondence No. 048: Amendment to protocol for Study 121.
8/31/93	Pharmos	FDA	Letter	IND Correspondence No. 049: Amendments to protocols for Studies 107 and 108.
9/14/93	Pharmos	FDA	Letter	IND Correspondence No. 050: Amendment to protocol for Study 122.
10/5/93	Pharmos	FDA	Letter	IND Correspondence No. 051: Amendment to protocols for Studies 107 and 108.
11/17/93	Pharmos	FDA	Letter	IND Correspondence No. 052: Amendments to protocols for Studies 107, 108, 121, and 122.
11/29/93	FDA-Tsu	Pharmos-Howes	Fax	Request for information on manufacturer, status of clinical trials, and drug substance impurities.
11/30/93	Pharmos-Howes	FDA-Tso		Response to Lotemax information request.
12/1/93	Pharmos	FDA	Letter	IND Correspondence No. 054: Amendments to protocols for Studies 121 and 122.
12/2/93	Pharmos	FDA		IND Correspondence No. 053: Response to 11/29/93 FDA fax.
2/3/94	Pharmos	FDA	Letter	IND Correspondence No. 055: IND Annual Report and Updated Investigator's Brochure.
2/22/94	Pharmos	FDA	Letter	IND Correspondence No. 056: Amendments to protocols for Studies 107, 121, and 122.
2/23/94	FDA-Joyce	Pharmos-Coultas	Fax	Draft questions from the Lotemax chemistry reviewer.
2/24/94	Pharmos-Coultas	FDA-Joyce	Letter	Notification that response to 2/23/98 FDA fax will be forthcoming.
3/18/94	Pharmos	FDA	Letter	IND Correspondence No. 057: Response to FDA microbiological questions.
5/13/94	Pharmos	FDA	Letter	IND Correspondence No. 058: Protocol for Study 120.
7/11/94	Pharmos-Howes	FDA-Joyce	Phone	Request for Lotemax Pre-NDA meeting.

FDA Correspondence Log

for the period 12/01/88 to 01/27/95

Date	From[1]	To[1]	Via	Subject
7/12/94	Pharmos-Howes	FDA-Childs	Letter	Request for Lotemax Pre-NDA meeting.
7/13/94	Pharmos-Howes	FDA-Joyce	Phone	Discussion concerning the agenda for the Lotemax Pre-NDA meeting.
8/31/94	Pharmos-Howes	FDA-Childs		Confirmation of 10/17/94 as meeting date.
10/21/94	Pharmos	FDA	Letter	IND Correspondence No. 060: Amendments to Form 1572s for Studies 107 and 122.
12/9/94	FDA-Chapman	B&L-Stoelzle	Letter	FDA acknowledgement of receipt of DMF.
1/12/95	Pharmos	FDA	Letter	IND Correspondence No. 061: FDA Pre-NDA meeting minutes.

FDA Correspondence Log

For the period 01/27/95 to 03/09/98

R

IND 32,432 **loteprednol etabonate ophthalmic suspension**
NDA 20-583 **Lotemax™ (loteprednol etabonate ophthalmic suspension), 0.5%**
NDA 20-803 **Alrex™ (loteprednol etabonate ophthalmic suspension), 0.2%**
NDA 20-841 **Lotemax™ (loteprednol etabonate ophthalmic suspension), 0.5% - Add'l Indications**

Date	From[1]	To[1]	Via	Subject
1/27/95	Pharmos-Howes	FDA	Letter	Early submission of Lotemax NDA Chemistry, Manufacturing, and Controls section under 21 CFR 314.50(d)(1)(iv).
3/29/95	Pharmos	FDA	Letter	Original Lotemax New Drug Application (NDA).
3/29/95	Pharmos-Howes	FDA-Chapman	Fax	Notification that disk copy of Lotemax NDA is being submitted.
3/29/95	Pharmos-Howes	FDA-Chapman	Fax	Notification that paper copy of Lotemax NDA is being submitted.
4/5/95	Pharmos-Howes	FDA-Chapman	Letter	Submission of additional copies of Lotemax study reports and disks.
4/13/95	Pharmos-Howes	FDA-Chapman	Fax	Submission of Lotemax small business exemption.
4/18/95	Pharmos-Howes	FDA-Gilman	Letter	Submission of list of Lotemax manufacturing sites ready for inspection.
4/24/95	B&L-Simmons	FDA-Gilman	Letter	Confirmation that B&L is the official testing site for the Lotemax NDA.
4/24/95	FDA-Gilman	B&L-Simmons	Phone	Discussion concerning DMFs referenced in the Lotemax NDA.
5/2/95	FDA-Chapman	Pharmos-Howes	Fax	Request that Lotemax NDA volumes be sent directly to Chapman.
5/2/95	Pharmos-Howes	FDA-Chapman	Fax	Notification that Lotemax NDA volumes are being sent to Chapman.
6/19/95	FDA-Chapman	Pharmos-Howes	Fax	Request for additional Lotemax information.
6/22/95	FDA-Chapman	Pharmos-Howes	Letter	List of Lotemax questions/comments.
6/23/95	Pharmos-Howes	FDA-Chapman	Phone	Discussion concerning Lotemax information requested by FDA.
6/23/95	FDA-Chapman	Pharmos-Howes		Request for additional Lotemax toxicology information.
6/26/95	Pharmos-Howes	FDA-Shriver	Fax	Response to June 22, 1995 request for Lotemax information.
6/29/95	Pharmos-Howes	FDA-Chapman	Letter	Submission of Lotemax NDA amendment.
7/10/95	Pharmos-Howes	FDA-Chapman, Shriver	Fax	Submission of revised Lotemax toxicology tables.
7/10/95	FDA-District	B&L-Bowman	Meeting	Pre-approval inspection for Lotemax (7/10/95 - 7/17/95).

Pharmos - Pharmos Corporation
B&L - Bausch & Lomb Pharmaceuticals, Inc., authorized agent for Pharmos Corporation

FDA Correspondence Log

For the period 01/27/95 to 03/09/98

Date	From[1]	To[1]	Via	Subject
7/18/95	FDA-Gilman	B&L-Simmons	Phone	Discussion concerning proposed meeting.
7/18/95	FDA-Gilman	B&L-Simmons	Phone	FDA request for process diagrams and copy of the Form-483 resulting from the recent FDA inspection.
7/18/95	FDA-Gilman	B&L-Simmons	Phone	Request for diagram of Lotemax manufacturing process.
7/19/95	B&L-Simmons	FDA-Gilman	Phone	Discussion concerning Lotemax samples.
7/20/95	B&L-Simmons	FDA-Hughes	Phone	Arrangements for phone conference between FDA and sponsor.
7/20/95	B&L-Simmons	FDA-Hughes	Phone	Request for phone conference regarding validation data for the Lotemax filling operation.
7/20/95	B&L-Howes	FDA-Chambers	Letter	Submission of Alrex protocol designs.
7/23/95	Pharmos	FDA	Letter	IND Correspondence No. 063: Amendment to protocol for Study 141.
7/24/95	FDA-Tolen	Pharmos-Riesenfeld	Letter	Lotemax NDA Not Approvable Letter.
7/24/95	FDA-Tolen	Pharmos-Riesenfeld	Letter	Lotemax pre-approval inspection report.
7/25/95	FDA-Cooney	B&L-Simmons	Phone	Request for Lotemax microbiology information.
7/25/95	B&L-Simmons	FDA-Cooney		Comments regarding the Lotemax NDA microbiology section.
7/29/95	Pharmos-Howes	FDA-Chapman	Letter	Submission of Lotemax NDA amendment.
7/31/95	Pharmos-Howes	FDA-Chapman	Phone	Clarification of certain statements made in the Lotemax NDA.
8/1/95	Pharmos-Howes	FDA-Tolen	Letter	Response to FDA Form 483 for Lotemax pre-approval inspection..
8/1/95	Pharmos-Howes	FDA-Tolen		Notification that additional manufacturing work will be needed to obtain Lotemax NDA approval.
8/2/95	Pharmos	FDA	Letter	IND Correspondence No. 064: IND Annual Report.
8/8/95	Pharmos-Howes	FDA-Gilman	Phone	Discussion on Lotemax GMP deficiencies.
8/21/95	FDA-Chapman	Pharmos-Howes	Fax	Request for pharmacology, toxicology, and chemistry sections of Lotemax NDA on diskette.
8/23/95	Pharmos-Howes	FDA-Chapman	Fax	Acknowledgement of above request.
8/25/95	FDA-Gilman	B&L-Simmons	E:mail	Request for information on Lotemax freeze-thaw studies.
8/29/95	Pharmos	FDA	Letter	IND Correspondence No. 145: Protocol for Study 145 - Dose Response.
8/30/95	Pharmos-Howes	FDA-Chapman	Letter	Submission of disks with Lotemax toxicology data.
9/8/95	Pharmos-Howes	FDA-Chapman		Notification that disks with Lotemax text, tables and figures are being sent.

FDA Correspondence Log

For the period 01/27/95 to 03/09/98

Date	From[1]	To[1]	Via	Subject
9/12/95	Pharmos	FDA	Letter	IND Correspondence No. 066: Amendment to protocol for Study 145.
9/20/95	FDA-Gilman	B&L-Simmons	E:mail	Request for FDA comment on plans to address Lotemax CMC deficiencies.
9/20/95	Pharmos-Howes	FDA-Chapman		Notification that Lotemax toxicology reports will be available in late October.
9/21/95	FDA-Gilman	B&L-Simmons	E:mail	Request for information on how to address change in Lotemax caps color and additional fill sizes.
10/12/95	Pharmos	FDA	Letter	IND Correspondence No. 067: Correction to protocol for Study 145.
10/22/95	Pharmos	FDA	Letter	IND Correspondence No. 068: Amendment to protocol for Study 145.
10/25/95	Pharmos	FDA	Letter	IND Correspondence No. 069: Protocols for Studies 143 and 144 - Seasonal Allergic Conjunctivitis.
11/10/95	B&L-Simmons	FDA-Childs	Letter	Submission of pre-meeting packages.
11/13/95	FDA-Gilman	Pharmos-Helton	E-Mail	Notification of Lotemax DMF deficiencies.
11/20/95	Pharmos	FDA	Letter	IND Correspondence No. 070: Additional Form 1572s for Studies 143 and 144.
11/20/95	Pharmos B&L	FDA-Chambers	Phone	Phone conference to discuss uveitis trials.
12/7/95	Pharmos	FDA	Letter	IND Correspondence No. 071: Additional CRF pages for Study 141.
12/10/95	Pharmos	FDA	Letter	IND Correspondence No. 072: Protocol for Study 126 - Comparison of the Safety and Efficacy of Loteprednol Etabonate in Acute Anterior Uveitis
12/12/95	B&L-Simmons, Howard	FDA-Chambers	Phone	Request for information on steroid class labeling.
12/12/95	FDA-Chambers	B&L-Simmons	Phone	Discussion concerning ophthalmic corticosteroid class labeling.
1/10/96	Pharmos-Howes	FDA-Wilkin	Letter	Discussion concerning a second uveitis study to obtain class labeling for Lotemax.
1/24/96	Pharmos	FDA	Letter	IND Correspondence No. 073: Amendment to protocol for Study 126 .
1/30/96	Pharmos-Howes	FDA-Chambers	Letter	Submission of Lotemax post cataract surgery draft protocols.
3/11/96	Pharmos-Helton	FDA-Chambers	Phone	Request for Lotemax NDA review status.
3/11/96	Pharmos-Howes	FDA-Chambers	Phone	Discussion concerning contact lens use and class labeling.
3/20/96	Pharmos	FDA	Letter	IND Correspondence No. 074: Authorization of Bausch & Lomb as agent for Pharmos Corporation. Protocols for Studies 125 and 127 - Treatment of Inflammation Following Cataract Surgery.
4/10/96	FDA-Weintraub	Pharmos-Howes	Letter	Not-approvable letter for Lotemax NDA.

FDA Correspondence Log

For the period 01/27/95 to 03/09/98

Date	From[1]	To[1]	Via	Subject
4/11/96	Pharmos	FDA	Letter	IND Correspondence No. 075: Changes to Form 1572s for Studies 125, 126, 127, and 143.
4/16/96	Pharmos-Howes	FDA-Chambers	Phone	Discussion concerning concomitant medications in proposed studies.
4/18/96	Pharmos-Helton	FDA-Gilman	Phone	Presentation of time table for responding to the April 10, 1996 Lotemax deficiency letter.
4/23/96	Pharmos	FDA	Letter	IND Correspondence No. 076: Amendments to protocols for Studies 125 and 126.
4/24/96	B&L-Simmons	FDA-Cook	Phone	Arrangements for phone conference with FDA.
4/24/96	FDA-Cooke	B&L-Simmons	Phone	Call to confirm May 30, 1996 meeting with FDA, Pharmos, and B&L.
5/6/96	FDA-Chambers	B&L-Simmons	Phone	Discussion concerning efficacy endpoints for uveitis and post-op studies.
5/6/96	FDA-Holmes	B&L-Simmons	Phone	Request for meeting with FDA and information on word processing software requirements.
5/6/96	FDA-Chambers	B&L-Simmons	Phone	Phone conference to discuss FDA recommendations regarding efficacy endpoints for uveitis and post-op studies.
5/16/96	B&L-Simmons	FDA-Chambers	Letter	Submission of minutes of 5/6/96 phone conference.
5/16/96	B&L-Simmons	FDA-Chambers	Letter	Request for meeting with FDA to discuss the 4/10/96 FDA letter.
5/30/96	B&L-Simmons	FDA-Chambers	Phone	Discussion regarding the 4/10/96 FDA letter.
5/31/96	Pharmos	FDA	Letter	IND Correspondence No. 077: Request for pre-NDA meeting for Alrex.
6/10/96	Pharmos	FDA	Letter	IND Correspondence No. 078: Additional Forms 1572s for Studies 125, 126, and 127.
6/14/96	B&L-Simmons	FDA-Chambers	Letter	Submission of comments on 5/30/96 discussion with FDA.
6/14/96	B&L-Simmons, Wysowskyj	FDA-Gilman	Phone	Request for information on ophthalmic product stability requirements.
6/14/96	B&L-Simmons	FDA-Chambers	Letter	Follow up letter from 5/30/96 FDA meeting.
6/14/96	B&L-Simmons	FDA-Gilman	Phone	Discussion concerning ophthalmic product stability.
6/24/96	B&L-Simmons	FDA-Chambers	Letter	Request for withdrawal of DMF 11226.
6/24/96	B&L-Simmons	FDA-Sheinin	Letter	Discussion of Lotemax stability program issues brought up during the May 30, 1996 FDA meeting.
7/30/96	B&L-Simmons	FDA-Chambers	Letter	Response to 4/10/96 FDA letter.
8/7/96	B&L	FDA	Letter	IND Correspondence No. 081: Summary of Pre-NDA meeting for Alrex.
8/27/96	FDA-District	B&L-Bowman	Meeting	Second pre-approval inspection for Lotemax (8/27/96 - 9/26/96).

FDA Correspondence Log

For the period 01/27/95 to 03/09/98

Date	From[1]	To[1]	Via	Subject
8/28/96	B&L-Simmons	FDA-Gilman	Phone	Notification that an electronic version of the Lotemax chemistry response is being sent.
10/21/96	FDA-Tolen	B&L-Dozier	Letter	Notification of completion of pre-approval inspection report and compliance with cGMPs.
11/21/96	Pharmos-Helton	FDA-Gilman	Phone	Request for Lotemax NDA review status.
11/25/96	B&L-Simmons	FDA-Committee	Phone	Discussion concerning proposed pre-clinical and clinical programs for other loteprednol etabonate products.
12/30/96	B&L-Simmons	FDA-Gilman	Phone	Discussion concerning planned SIPSY DMF amendment
1/25/97	Pharmos	FDA	Letter	IND Correspondence No. 083: Additional Form 1572s for Studies 125, 126, and 127.
1/30/97	B&L-Simmons	FDA-Gilman	Phone	Discussion concerning review of Lotemax 7/30/96 deficiency response.
1/31/97	B&L-Simmons	FDA-	Letter	Filing of NDA 20-583 for Alrex,
2/12/97	FDA-LoBianco	B&L-Simmons	Letter	Acknowledgement of receipt of NDA 20-803 for Alrex.
2/14/97	Pharmos	FDA	Letter	IND Correspondence No. 084: IND Annual Report.
2/21/97	B&L-Simmons	FDA-Chambers	Letter	Submission of Lotemax stability update.
2/24/97	Pharmos-Riesenfeld	FDA-Holmes	Letter	Authorization for B&L to contact FDA on Pharmos' behalf.
2/25/97	B&L-Simmons	FDA-Gilman	Phone	Request for Lotemax and Alrex NDA review status.
2/26/97	Pharmos	FDA	Letter	IND Correspondence No. 085: IND Annual Report
3/7/97	B&L-Simmons	FDA-Chambers	Letter	Final response to Lotemax 4/10/96 Not Approvable Letter.
3/7/97	B&L-Simmons	FDA-Chambers	Letter	Filing of NDA 20-841.
3/17/97	FDA-LoBianco	Pharmos-Simmons	Letter	Acknowledgment of receipt of amendment to NDA 20-841.
3/17/97	B&L-Simmons Wysowskyj	FDA	Phone	Request for Lotemax and Alrex NDA review status.
3/21/97	B&L-Simmons	FDA-Gilman	Phone	Discussion concerning samples, methods validation information, and additional fill sizes.
3/27/97	B&L	FDA	Letter	IND Correspondence No. 086: Protocol for Study BLP-001: Overview of clinical investigations.
3/27/97	B&L-Simmons, Wysowskyj	FDA-Homes, Hughes	Phone	Discussion concerning microbiology, clinical audits, labeling, and pilot studies.
4/1/97	B&L-Simmons	FDA-Tolen	Letter	Submission of the field copy of the 7/30/96 Lotemax submission.
4/1/97	B&L-Wysowskyj	FDA-Gilman	Fax & Letter	Response to request for information on Lotemax trademark search.

FDA Correspondence Log

For the period 01/27/95 to 03/09/98

Date	From[1]	To[1]	Via	Subject
4/2/97	B&L-Wysowskyj	FDA-Holmes, Fenselau	Phone	Request for Lotemax and Alrex NDA review status.
4/9/97	B&L-Simmons	FDA-Gilman	Phone	Request for Lotemax CMC review status.
4/25/97	B&L-Wysowskyj	FDA-Fenselau	Phone	Request for Lotemax and Alrex NDA review status.
5/2/97	B&L-Simmons	FDA-Gilman, Holmes	Phone	Request for Lotemax NDA review status.
5/7/97	B&L-Simmons	FDA-Gilman, Holmes	Phone	Request for Lotemax and Alrex NDA review status.
5/13/97	B&L-Wysowskyj	FDA-Gunter	Phone	Request for status of FDA trade name review.
5/16/97	B&L-Simmons	FDA-Rumble	Phone	Notification that Lotemax promotional campaign will be submitted shortly.
6/4/97	B&L-Wysowskyj	FDA-Chambers	Letter	Revised Lotemax draft labeling.
6/6/97	FDA-LoBianco	B&L-Simmons	Letter	Notification that all required fees were received and application accepted 5/2/97 for second Lotemax NDA.
6/6/97	B&L-Wysowskyj	FDA-Gunter	Phone	Request for Lotemax and Alrex NDA review status. Discussion concerning product packaging.
6/16/97	B&L-Simmons	FDA-Chambers	Letter	Request for Lotemax and Alrex NDA review status.
6/25/97	B&L-Wysowskyj	FDA-Gunter	Phone	Request for Lotemax and Alrex NDA review status.
6/25/97	FDA-District	B&L-Bowman	Meeting	Pre-approval inspection for Alrex (6/25/97 - 7/9/97).
7/21/97	B&L-Strahlman	FDA-Chambers	Phone	Request for Lotemax and Alrex NDA review status.
8/4/97	FDA-Chambers	B&L-Simmons	Phone	Lotemax and Alrex NDA review status update.
8/4/97	FDA-Chambers	B&L-Simmons	Phone	Discussion concerning Lotemax labeling.
8/8/97	B&L-Simmons	FDA-Gunter	Phone	Discussion concerning outstanding Lotemax CMC issues.
8/8/97	B&L-Simmons	FDA-Gunter	Phone	Request that B&L be included in any Lotemax or Alrex chemistry review discussions.
8/14/97	B&L-Simmons	FDA-Chambers	Phone	Discussion concerning outstanding Lotemax and Alrex CMC issues.
8/14/97	FDA-Chambers	B&L-Strahlman	Fax	Submission of proposal for Lotemax labeling.
8/20/97	B&L-Simmons	FDA-Chambers	Letter	Response to FDA requests made during 8/14/97 phone conference.
8/22/97	B&L-Simmons	FDA-Holmes	Fax & Letter	Request for FDA comment on Lotemax and Alrex draft labeling.

FDA Correspondence Log

For the period 01/27/95 to 03/09/98

Date	From[1]	To[1]	Via	Subject
9/3/97	FDA-Weintraub	B&L-Simmons	Letter	Lotemax NDA Approvable Letter.
9/18/97	B&L-Simmons	FDA-Gunter	Letter	Initial response to 9/3/97 Approvable Letter.
10/16/97	B&L-Wysowskyj	FDA-LoBianco	Phone	Notification of new FDA review coordinator.
11/5/97	B&L-Wysowskyj	FDA-LoBianco	Phone	Request for Lotemax and Alrex NDA review status.
11/10/97	B&L-Simmons	FDA-Chambers	Letter	Partial response to 9/3/97 Lotemax Approvable Letter.
11/11/97	B&L-Simmons	FDA-Chambers	Letter	Partial response to 9/3/97 Lotemax Approvable Letter.
12/10/97	B&L-Wysowskyj	FDA-Chambers	Letter	Partial response to 9/3/97 Lotemax Approvable Letter.
12/11/97	B&L-Wysowskyj	FDA-Chambers	Letter	Partial response to 9/3/97 Lotemax Approvable Letter.
12/15/97	B&L-Wysowskyj	FDA-Tolen	Letter	Field Copy of 12/10/97 submission.
12/15/97	B&L-Simmons	FDA-Chambers	Phone	Discussion concerning Lotemax product labeling.
12/16/97	B&L-Wysowskyj	FDA-Chambers	Letter	Partial response to 9/3/97 Lotemax Approvable Letter.
12/19/97	B&L-Wysowskyj	FDA-Fenselau	Phone	Discussion concerning CMC issues included in 9/3/97 NDA Approvable Letter.
12/22/97	B&L-Wysowskyj	FDA-Fenselau	Phone	Request for Lotemax and Alrex NDA review status.
12/23/97	Pharmos	FDA	Letter	IND Correspondence No. 087: Change of address for Pharmos Corporation.
1/8/98	B&L-Simmons	FDA-Chambers	Letter	Revised Lotemax draft labeling.
1/8/98	FDA-LoBianco	B&L-Wysowskyj	Fax & Letter	FDA request for additional Alrex CMC information.
1/9/98	B&L-Wysowskyj	FDA-LoBianco	Fax & Letter	Responses to FDA's 1/8/98 CMC questions.
1/14/98	B&L-Simmons	FDA-Chambers	Letter	Submission of draft labeling faxed to FDA on 1/8/98.
1/17/98	B&L-Wysowskyj	FDA-Chambers	Phone	Request for Lotemax and Alrex NDA review status.
1/21/98	B&L-Simmons	FDA-Chambers	Letter	Revised Lotemax draft labeling.
1/22/98	B&L-Simmons	FDA-Baylor-Henry	Letter	Submission of initial Lotemax promotional campaign for DDMAC comment.
1/30/98	B&L-Wysowskyj	FDA-Fenselau	Phone	Request for status of Lotemax and Alrex reviews.
2/5/98	B&L-Wysowskyj	FDA-LoBianco Chambers	Phone	Discussion concerning FDA request for Lotemax microbiology information.

FDA Correspondence Log

For the period 01/27/95 to 03/09/98

Date	From[1]	To[1]	Via	Subject
2/5/98	FDA-LoBianco	B&L-Wysowskyj	Phone	Notification that FDA would be sending fax regarding Lotemax NDA microbiology section.
2/9/98	B&L-Wysowskyj	FDA-Chambers	Letter	Response to 2/5/98 FDA request for Lotemax microbiology information.
2/11/98	FDA-Rumble	B&L-Simmons	Letter	DDMAC observations on Lotemax promotional materials.
2/12/98	B&L-Simmons	FDA -Patel	Phone	Request for status of Lotemax and Alrex reviews.
2/17/98	FDA-Chambers	B&L-Simmons	Letter	Acknowledgment of original Lotemax NDA filed June 9, 1995.
2/23/98	FDA-Chambers	B&L-Simmons	Fax	Request for changes to Lotemax labeling.
2/23/98	FDA-Chambers	B&L-Simmons	Fax	Request for changes to Lotemax labeling.
2/24/98	B&L-Wysowskyj	FDA-Chambers	Letter	Submission of revised Lotemax draft labeling, safety update, and Phase IV commitments.
2/25/98	B&L-Wysowskyj	FDA-Chambers	Letter	Submission of revised Alrex regulatory specification, draft labeling, safety update, and Phase IV commitments.
2/26/98	B&L-Wysowskyj	FDA-Chambers	Letter	Submission of revised draft Alrex labeling.
3/3/98	B&L-Wysowskyj	FDA-Chambers	Letter	Submission of revised draft Alrex labeling.
3/6/98	B&L-Wysowskyj	FDA-Chambers	Letter	Submission of revised draft Lotemax and Alrex labeling.
3/6/98	FDA-Chambers	B&L-Wysowskyj	Fax	Request for changes to Lotemax labeling.
3/9/98	B&L-Simmons	FDA-Chambers	Letter	Submission of revised draft Alrex labeling.
3/9/98	FDA-Weintraub	B&L-Simmons	Letter	Approval of NDAs 20-583, 20-841, and 20-803 for Lotemax and Alrex.

Loteprednol Etabonate Ophthalmic Suspension

Adequate and Well-Controlled Clinical Studies Essential to the Demonstration of Safety and Efficacy of the Approved Products

No.	Study	Final Report Date	First Patient In	Last Patient Out	Study Drugs
107-GPC	Safety and Efficacy of Loteprednol Etabonate in Giant Papillary Conjunctivitis	09/94	05/24/93	04/11/94	0.5% Placebo
108-GPC	Safety and Efficacy of Loteprednol Etabonate in Giant Papillary Conjunctivitis	08/94	05/25/93	02/14/94	0.5% Placebo
121-SAC	Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis	11/94	08/09/93	01/31/94	0.5% Placebo
122-U	Safety and Efficacy of Loteprednol Etabonate in Acute Anterior Uveitis	03/95	10/13/93	09/29/94	0.5% Prednisolone Acetate 1%
125-PO	Safety and Efficacy of Loteprednol Etabonate in Inflammation Following Cataract Surgery with Intraocular Lens Implantation	02/97	05/16/96	09/12/96	0.5% Placebo
126-U	Safety and Efficacy of Loteprednol Etabonate in Acute Anterior Uveitis	03/97	01/26/96	10/07/96	0.5% Prednisolone Acetate 1%
127-PO	Safety and Efficacy of Loteprednol Etabonate in Inflammation Following Cataract Surgery	02/97	05/23/96	10/18/96	0.5% Placebo
143-SAC	Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis	08/96	12/19/95	03/09/96	0.2% Placebo
144-SAC	Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis	08/96	12/18/95	03/09/96	0.2% Placebo

Loteprednol Etabonate Ophthalmic Suspension

Adequate and Well-Controlled Clinical Studies Essential to the Demonstration of Safety and Efficacy of the Approved Products

No.	Study	Final Report Date	First Patient In	Last Patient Out	Study Drugs
107-GPC	Safety and Efficacy of Loteprednol Etabonate in Giant Papillary Conjunctivitis	09/94	05/24/93	04/11/94	0.5% Placebo
108-GPC	Safety and Efficacy of Loteprednol Etabonate in Giant Papillary Conjunctivitis	08/94	05/25/93	02/14/94	0.5% Placebo
121-SAC	Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis	11/94	08/09/93	01/31/94	0.5% Placebo
122-U	Safety and Efficacy of Loteprednol Etabonate in Acute Anterior Uveitis	03/95	10/13/93	09/29/94	0.5% Prednisolone Acetate 1%
125-PO	Safety and Efficacy of Loteprednol Etabonate in Inflammation Following Cataract Surgery with Intraocular Lens Implantation	02/97	05/16/96	09/12/96	0.5% Placebo
126-U	Safety and Efficacy of Loteprednol Etabonate in Acute Anterior Uveitis	03/97	01/26/96	10/07/96	0.5% Prednisolone Acetate 1%
127-PO	Safety and Efficacy of Loteprednol Etabonate in Inflammation Following Cataract Surgery	02/97	05/23/96	10/18/96	0.5% Placebo
143-SAC	Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis	08/96	12/19/95	03/09/96	0.2% Placebo
144-SAC	Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis	08/96	12/18/95	03/09/96	0.2% Placebo

Loteprednol Etabonate Ophthalmic Suspension

Selected Other Studies Carried Out To Support Approval

No.	Study	Final Report Date	First Patient In	Last Patient Out	Study Drugs
106-GPC	Pilot Efficacy of Loteprednol Etabonate in Giant Papillary Conjunctivitis	03/92	09/07/90	01/22/91	0.5% Placebo
PTC-74	52 Week Ocular Toxicity in the Dog	04/92	02/90	03/91	0.05% 0.1% 0.5% Placebo
104-CPT	Loteprednol Etabonate Dose Response in Conjunctival Provocation Test	07/92	03/28/90	05/07/90	0.1% 0.5%
PHA-32	Effect of Loteprednol Etabonate on Aero Allergen Induced Bronchial Eosinophilia in the Guinea Pig	12/18/92	N/A	N/A	N/A
105-CPT	Pilot Efficacy of Loteprednol Etabonate in Conjunctival Provocation	03/93	10/11/90	11/21/90	0.5% Prednisolone Acetate 1% Placebo
1120-5050-03	Delayed Contact Hypersensitivity in the Guinea Pig	03/05/93	01/11/93	01/20/93	0.5% Cream
103-SR	Safety of Loteprednol Etabonate Affect on Intraocular Pressure in Known Steroid Responsive Individuals	08/93	10/31/90	07/24/91	0.5% Prednisolone Acetate 1%
114-SAC	Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis (discontinued)	03/94	12/19/90	03/22/91	0.5% Placebo
PTC-89	26 Week Ocular Toxicity in the Rabbit	11/94	06/93	12/93	0.5% Placebo
A/E 40367	Loteprednol Etabonate Degradation Product PJ-90 Primary Eye Irritation in the Rabbit	04/94	N/A	N/A	PJ-90 0.5%
141-AC	Validation of Antigen Challenge Model Using Loteprednol Etabonate	02/96	08/03/95	09/14/95	0.5% Placebo
145-DR	Loteprednol Etabonate Dose Response	03/96	10/95	11/95	0.1% 0.2% 0.3% 0.5% Placebo

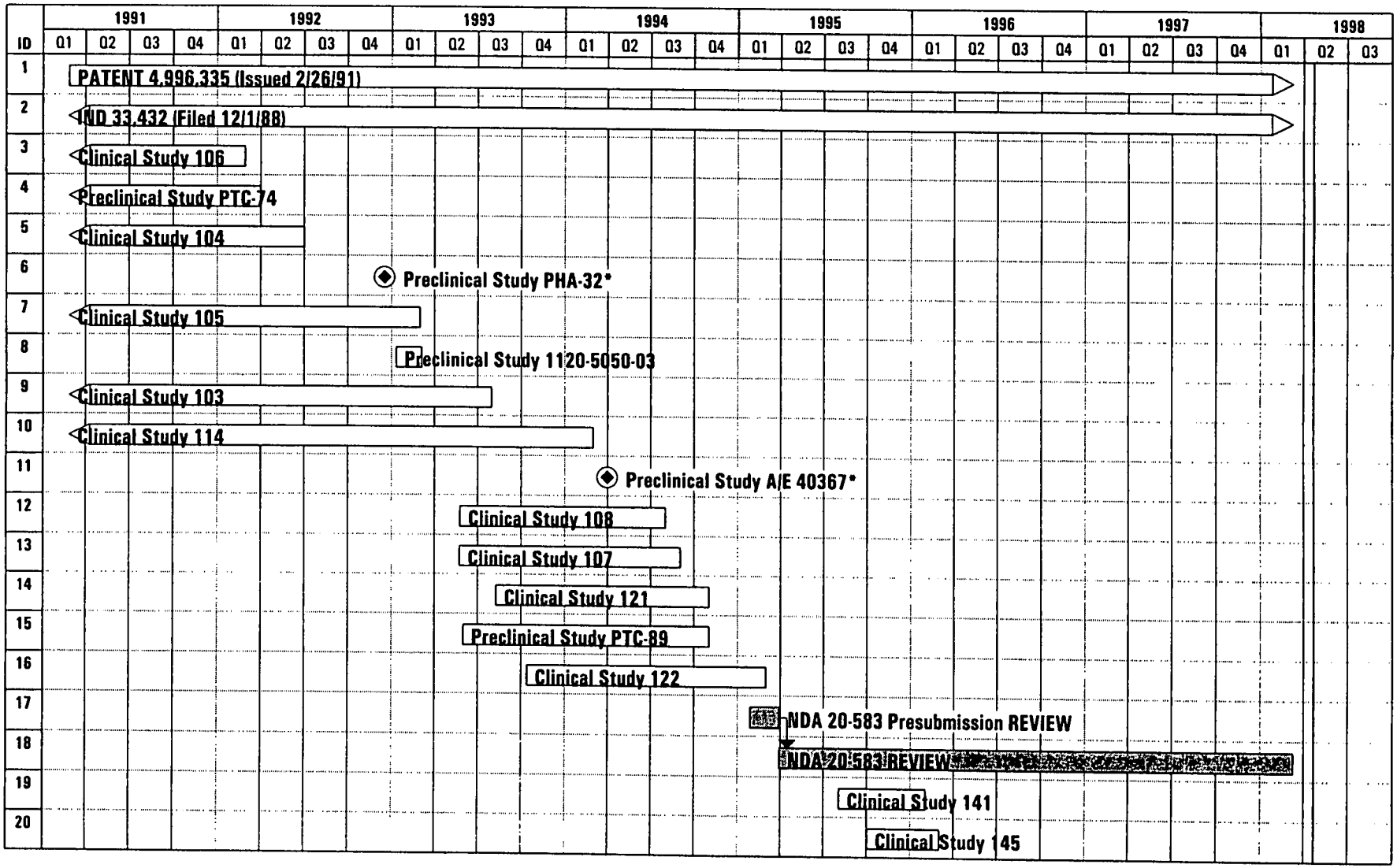
Loteprednol Etabonate Ophthalmic Suspension

Selected Other Studies Carried Out To Support Approval

No.	Study	Final Report Date	First Patient In	Last Patient Out	Study Drugs
106-GPC	Pilot Efficacy of Loteprednol Etabonate in Giant Papillary Conjunctivitis	03/92	09/07/90	01/22/91	0.5% Placebo
PTC-74	52 Week Ocular Toxicity in the Dog	04/92	02/90	03/91	0.05% 0.1% 0.5% Placebo
104-CPT	Loteprednol Etabonate Dose Response in Conjunctival Provocation Test	07/92	03/28/90	05/07/90	0.1% 0.5%
PHA-32	Effect of Loteprednol Etabonate on Aero Allergen Induced Bronchial Eosinophilia in the Guinea Pig	12/18/92	N/A	N/A	N/A
105-CPT	Pilot Efficacy of Loteprednol Etabonate in Conjunctival Provocation	03/93	10/11/90	11/21/90	0.5% Prednisolone Acetate 1% Placebo
1120-5050-03	Delayed Contact Hypersensitivity in the Guinea Pig	03/05/93	01/11/93	01/20/93	0.5% Cream
103-SR	Safety of Loteprednol Etabonate Affect on Intraocular Pressure in Known Steroid Responsive Individuals	08/93	10/31/90	07/24/91	0.5% Prednisolone Acetate 1%
114-SAC	Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis (discontinued)	03/94	12/19/90	03/22/91	0.5% Placebo
PTC-89	26 Week Ocular Toxicity in the Rabbit	11/94	06/93	12/93	0.5% Placebo
A/E 40367	Loteprednol Etabonate Degradation Product PJ-90 Primary Eye Irritation in the Rabbit	04/94	N/A	N/A	PJ-90 0.5%
141-AC	Validation of Antigen Challenge Model Using Loteprednol Etabonate	02/96	08/03/95	09/14/95	0.5% Placebo
145-DR	Loteprednol Etabonate Dose Response	03/96	10/95	11/95	0.1% 0.2% 0.3% 0.5% Placebo

Loteprednol Etabonate Ophthalmic Suspensions

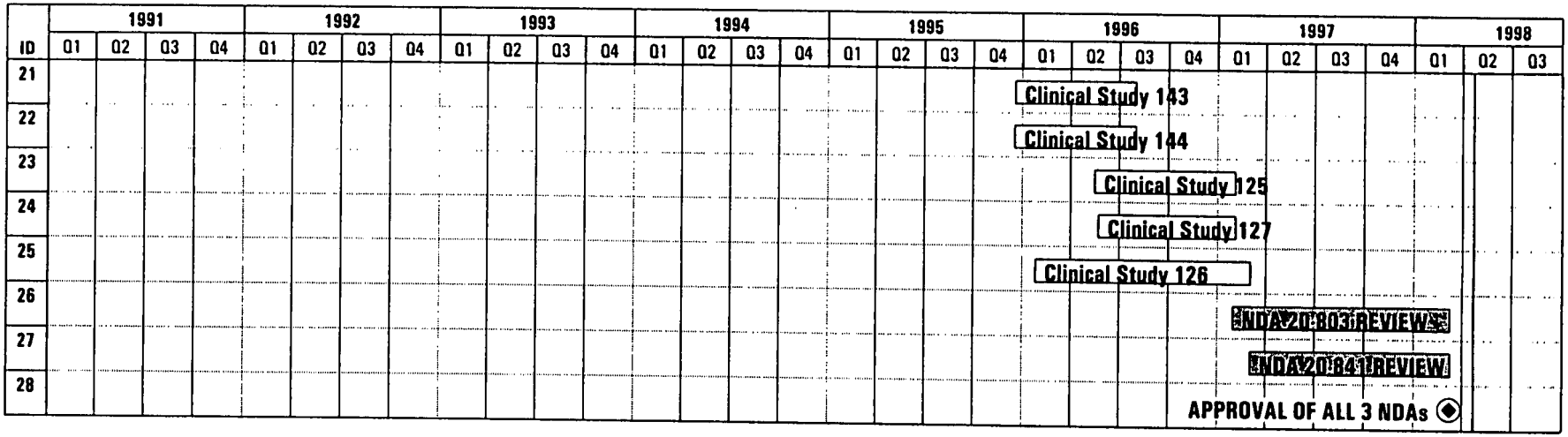
Time Spent Conducting & Analyzing Selected Pivotal and Supportive Preclinical and Clinical Studies



* Start and end dates are not available for these studies. Only the date of the final report is noted.

Loteprednol Etabonate Ophthalmic Suspensions

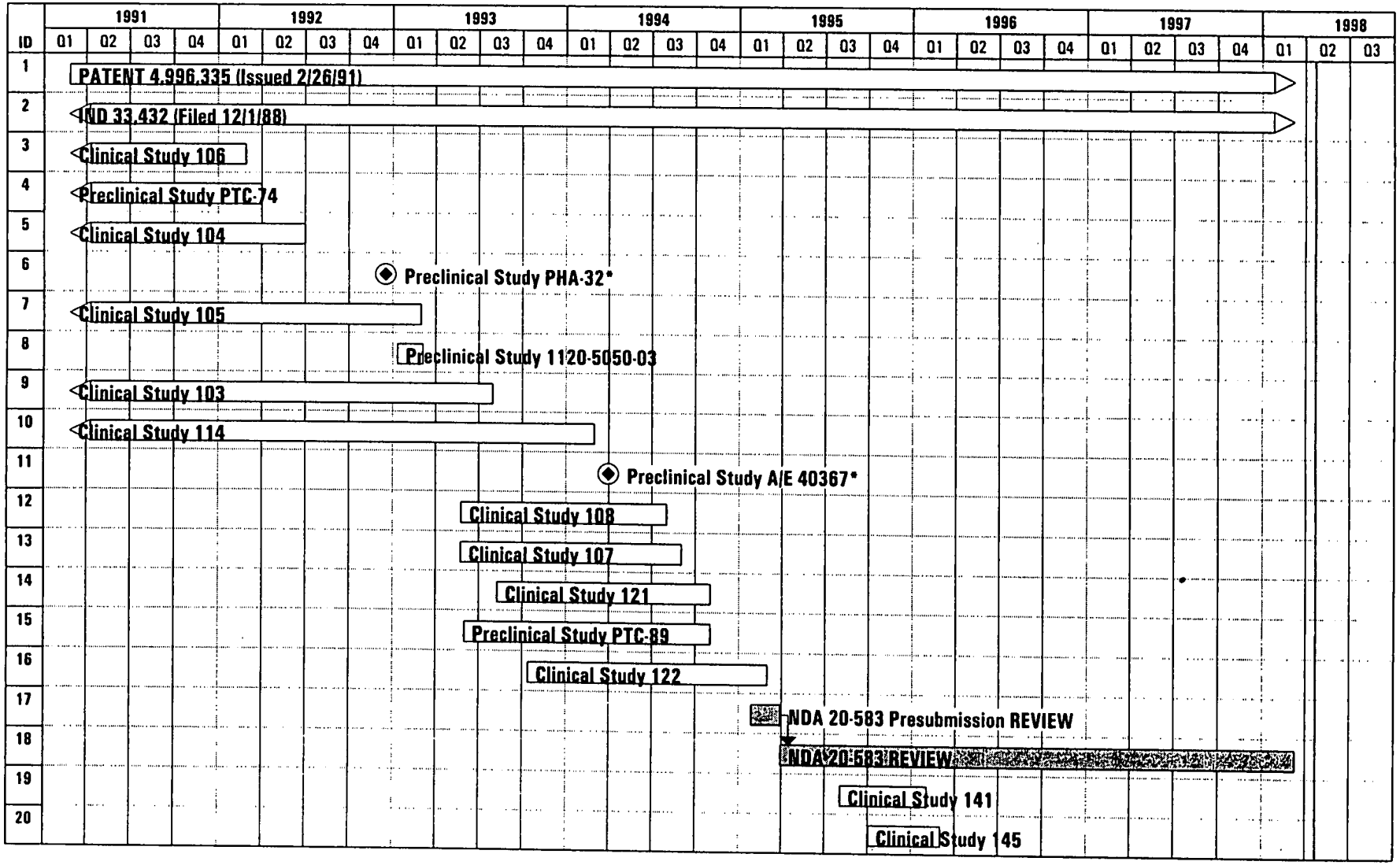
Time Spent Conducting & Analyzing Selected Pivotal and Supportive Preclinical and Clinical Studies



* Start and end dates are not available for these studies. Only the date of the final report is noted.

Loteprednol Etabonate Ophthalmic Suspensions

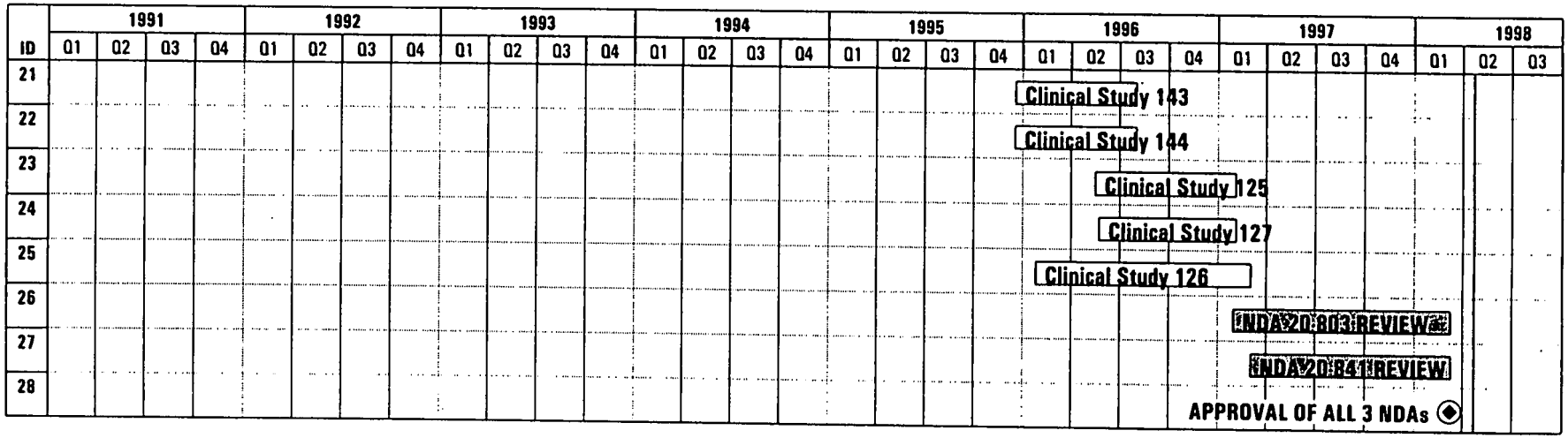
Time Spent Conducting & Analyzing Selected Pivotal and Supportive Preclinical and Clinical Studies



* Start and end dates are not available for these studies. Only the date of the final report is noted.

Loteprednol Etabonate Ophthalmic Suspensions

Time Spent Conducting & Analyzing Selected Pivotal and Supportive Preclinical and Clinical Studies



* Start and end dates are not available for these studies. Only the date of the final report is noted.